Fig. 1

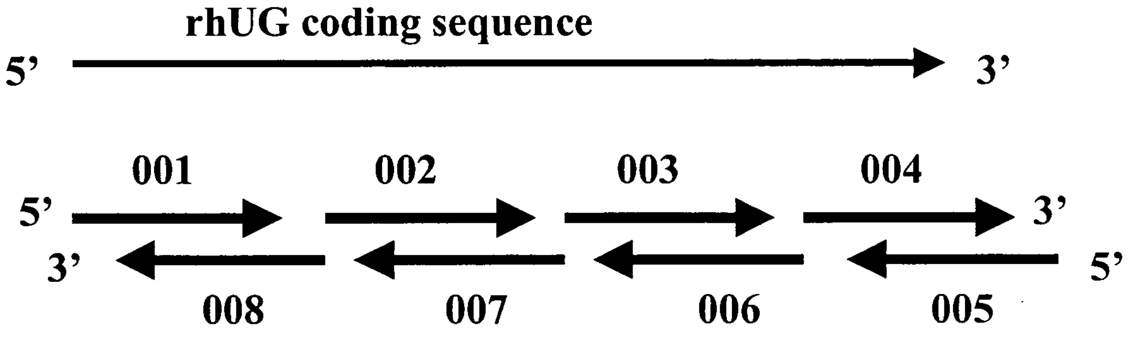
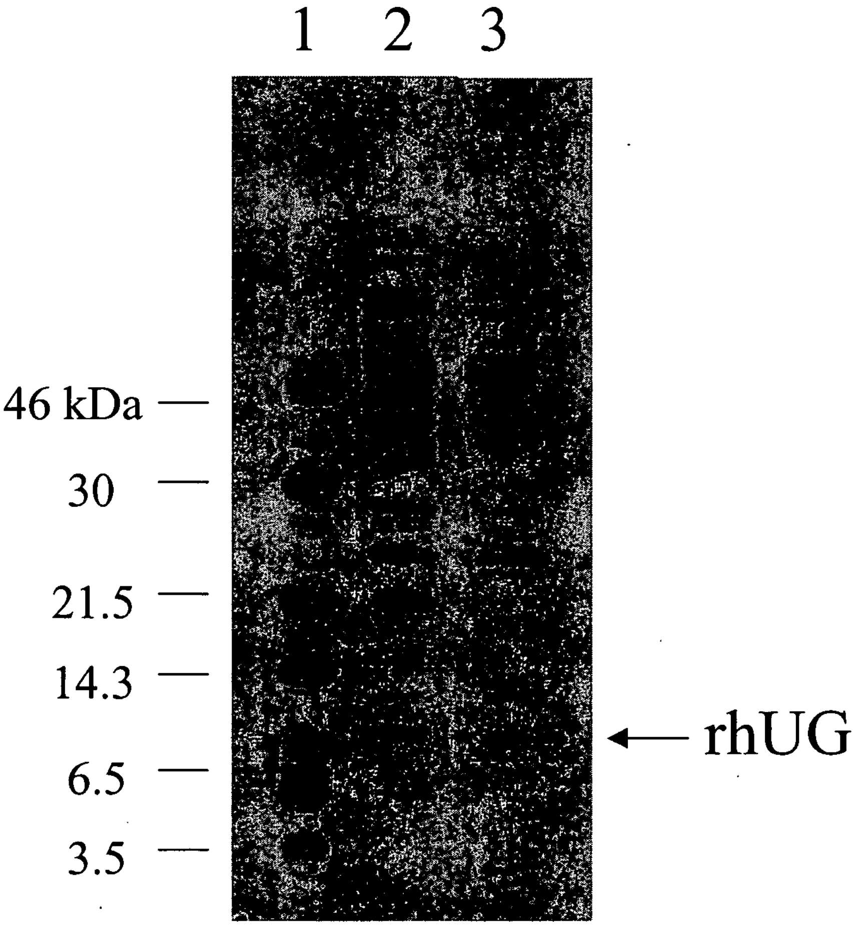
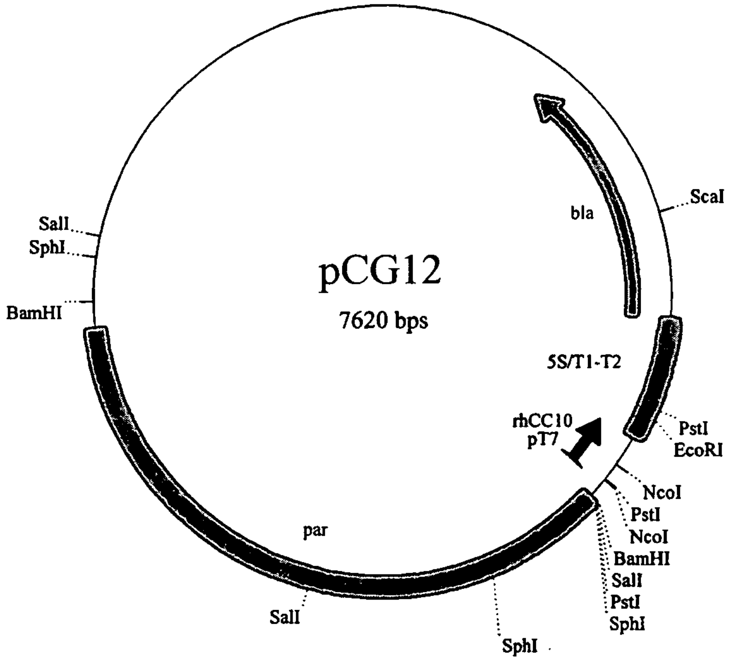

rhUG coding sequence
5'
3'
001
002
003
004
5'
3'
3'
5'
008
007
006
005

Fig. 2


1
2
3
46 kDa
30
21.5
14.3
6.5
3.5
rhUG

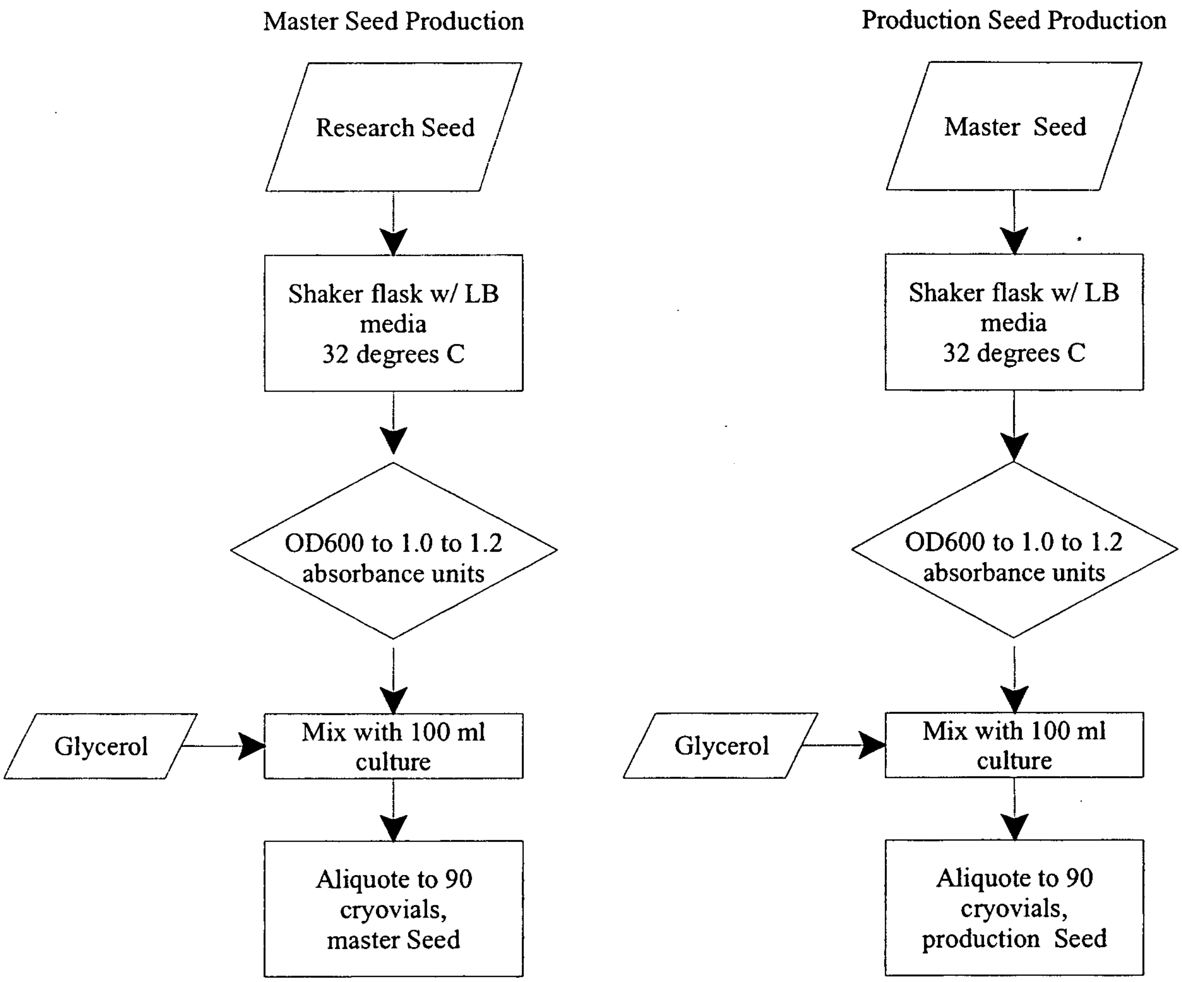
09895646.070201

Fig. 3


pCG12
7620 bps
bla
ScaI
5S/T1-T2
PstI
EcoRI
rhCC10
pT7
NcoI
PstI
NcoI
BamHI
SalI
PstI
SphI
SphI
SalI
par
BamHI
SphI
SalI

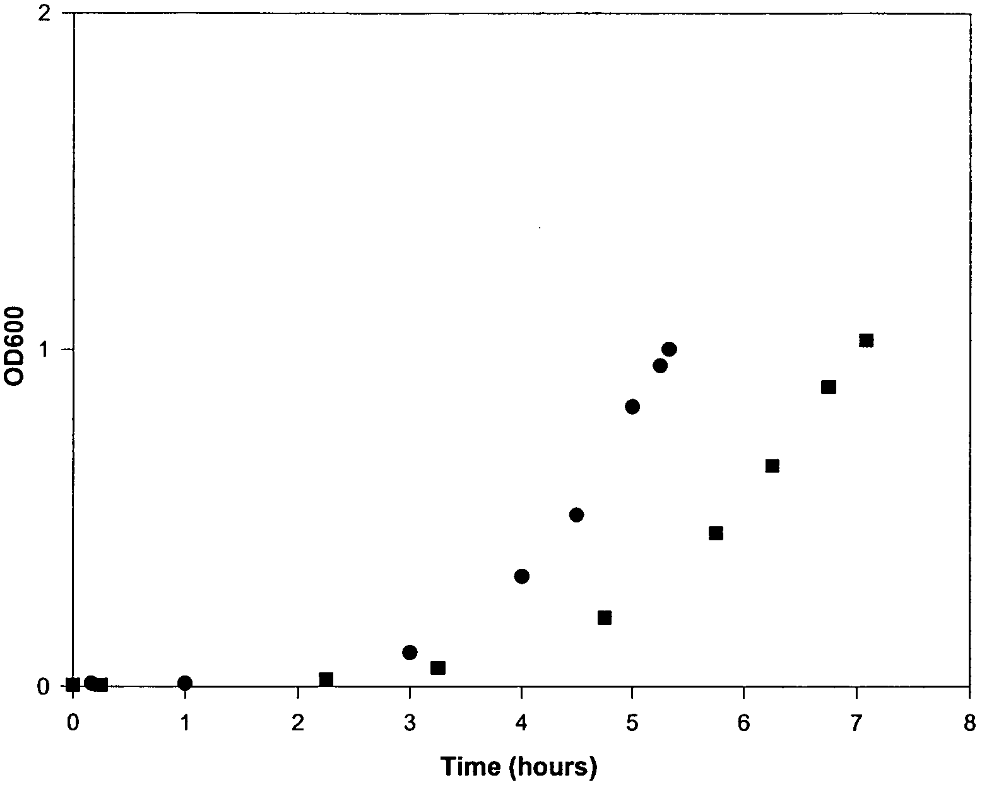
09806516.072601

Fig. 4


Master Seed Production
Research Seed
Shaker flask w/ LB media 32 degrees C
OD600 to 1.0 to 1.2 absorbance units
Glycerol
Mix with 100 ml culture
Aliquote to 90 cryovials, master Seed
Production Seed Production
Master Seed
Shaker flask w/ LB media 32 degrees C
OD600 to 1.0 to 1.2 absorbance units
Glycerol
Mix with 100 ml culture
Aliquote to 90 cryovials, production Seed

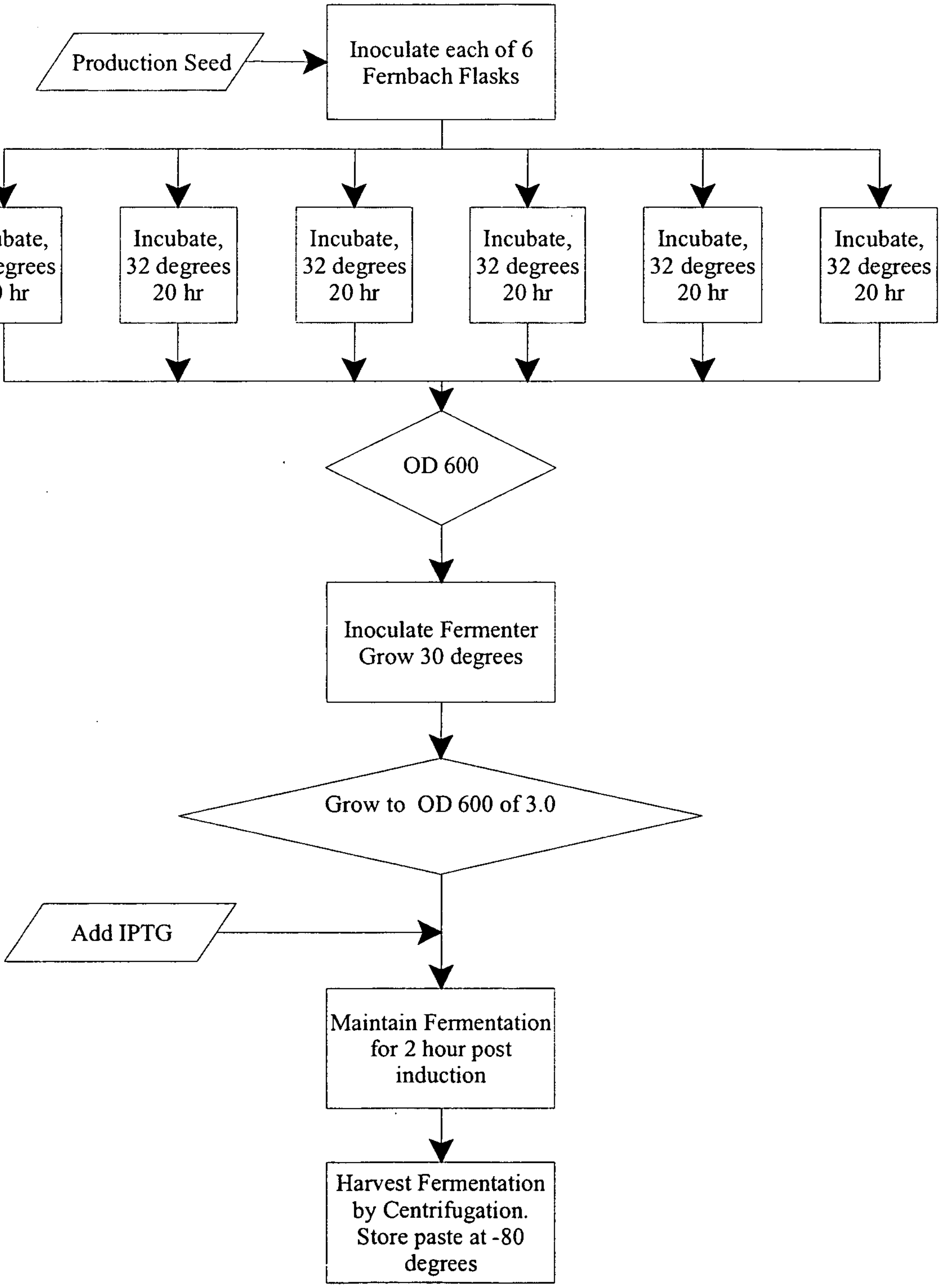
09856415 .070201

Fig. 5



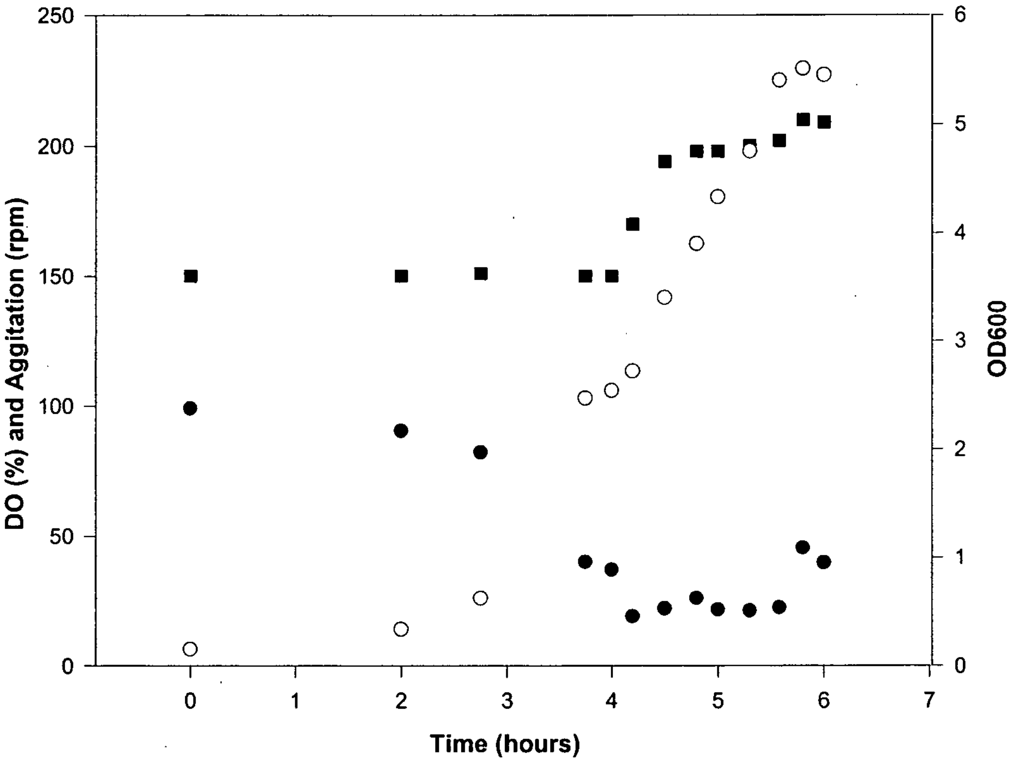
10020407.051502

Fig. 6


Production Seed
Inoculate each of 6 Fernbach Flasks
Incubate, 32 degrees 20 hr
Incubate, 32 degrees 20 hr
Incubate, 32 degrees 20 hr
Incubate, 32 degrees 20 hr
Incubate, 32 degrees 20 hr
Incubate, 32 degrees 20 hr
OD 600
Inoculate Fermenter Grow 30 degrees
Grow to OD 600 of 3.0
Add IPTG
Maintain Fermentation for 2 hour post induction
Harvest Fermentation by Centrifugation. Store paste at -80 degrees

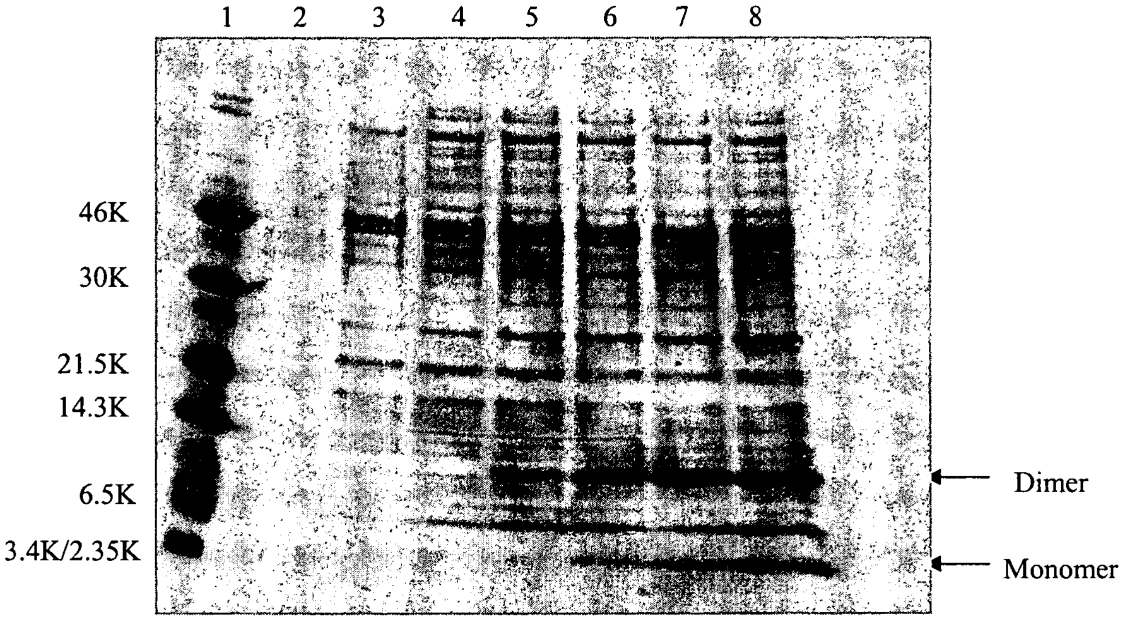
09806715 .072001

Fig. 7



10020705.051502

Fig. 8


1
2
3
4
5
6
7
8
46K
30K
21.5K
14.3K
6.5K
3.4K/2.35K
Dimer
Monomer

10020207.091865001

Fig. 9a

Purification used in Initial Toxicology study

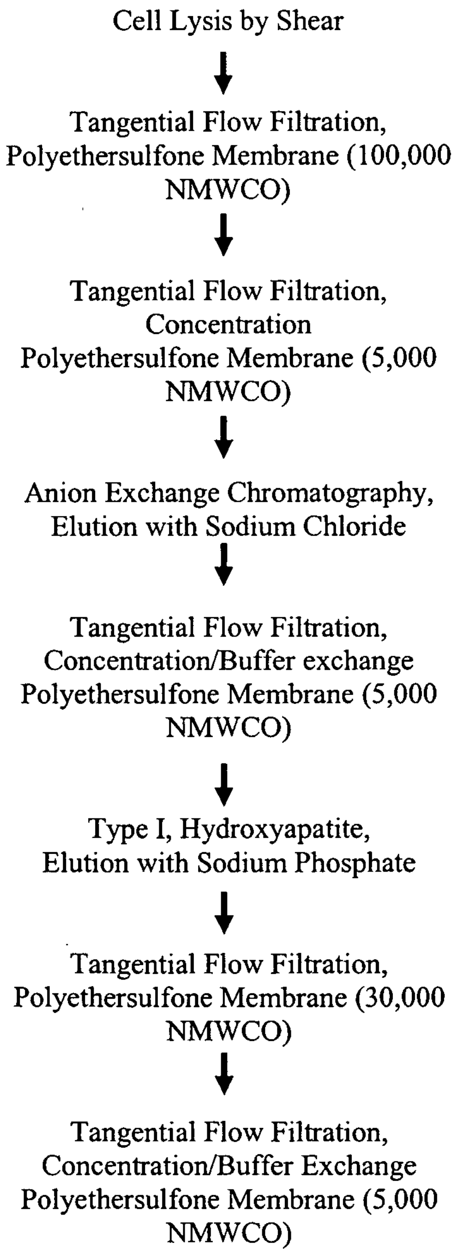

Cell Lysis by Shear
Tangential Flow Filtration, Polyethersulfone Membrane (100,000 NMWCO)
Tangential Flow Filtration, Concentration Polyethersulfone Membrane (5,000 NMWCO)
Anion Exchange Chromatography, Elution with Sodium Chloride
Tangential Flow Filtration, Concentration/Buffer exchange Polyethersulfone Membrane (5,000 NMWCO)
Type I, Hydroxyapatite, Elution with Sodium Phosphate
Tangential Flow Filtration, Polyethersulfone Membrane (30,000 NMWCO)
Tangential Flow Filtration, Concentration/Buffer Exchange Polyethersulfone Membrane (5,000 NMWCO)

Fig. 9b

Purification used in first cGMP Manufacturing Run

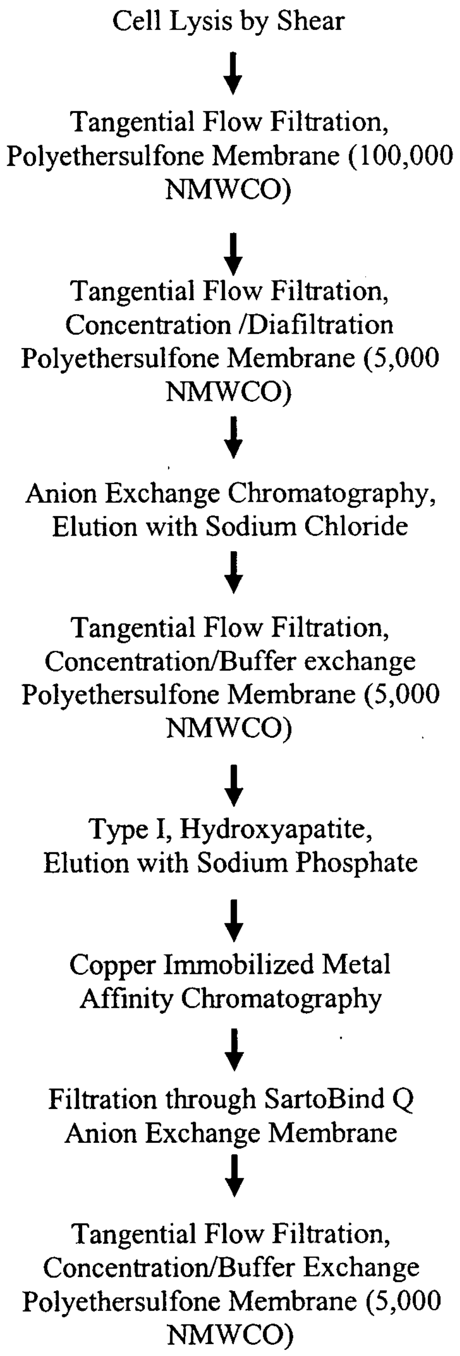

Cell Lysis by Shear
Tangential Flow Filtration, Polyethersulfone Membrane (100,000 NMWCO)
Tangential Flow Filtration, Concentration /Diafiltration Polyethersulfone Membrane (5,000 NMWCO)
Anion Exchange Chromatography, Elution with Sodium Chloride
Tangential Flow Filtration, Concentration/Buffer exchange Polyethersulfone Membrane (5,000 NMWCO)
Type I, Hydroxyapatite, Elution with Sodium Phosphate
Copper Immobilized Metal Affinity Chromatography
Filtration through SartoBind Q Anion Exchange Membrane
Tangential Flow Filtration, Concentration/Buffer Exchange Polyethersulfone Membrane (5,000 NMWCO)

Fig. 10

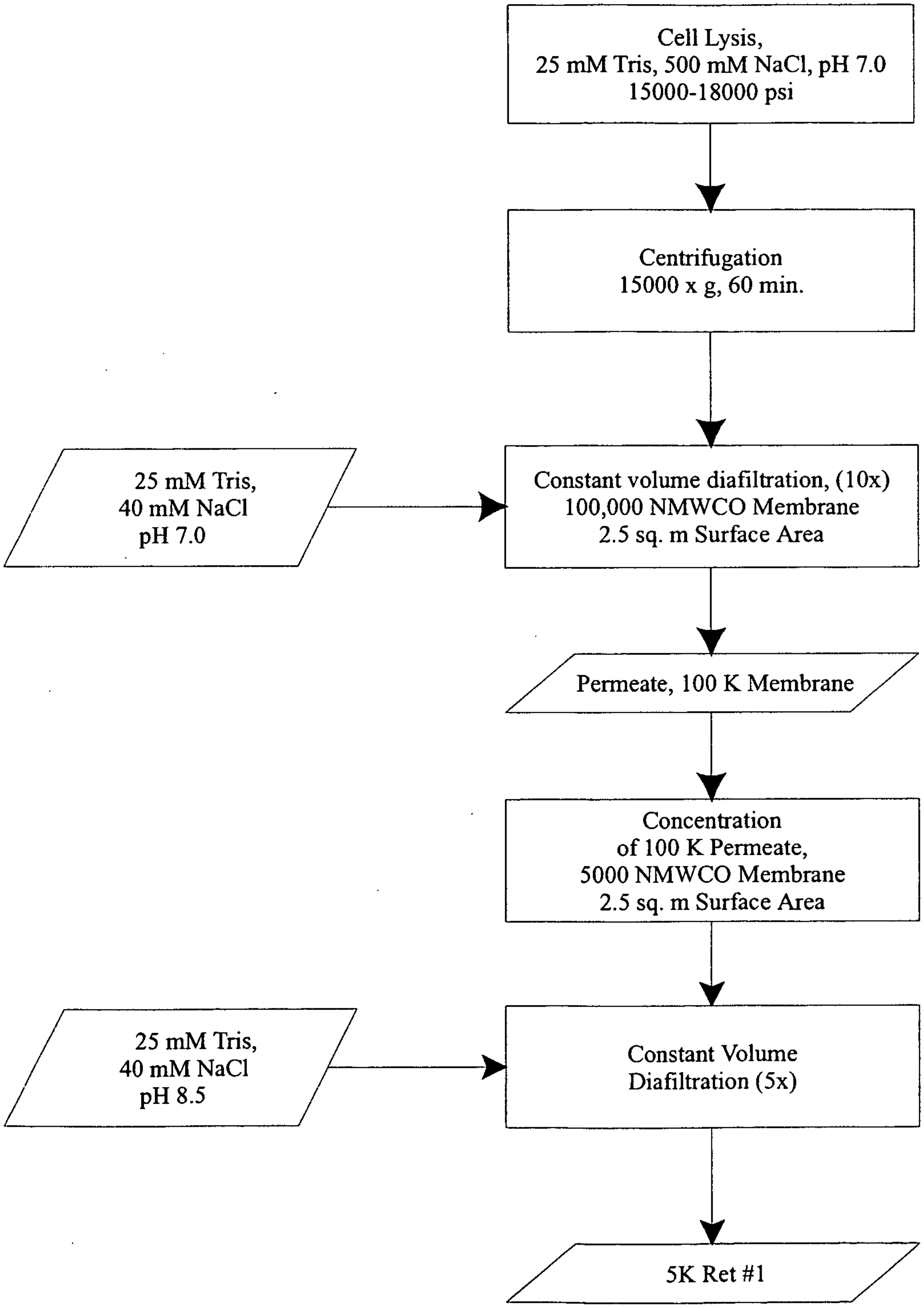
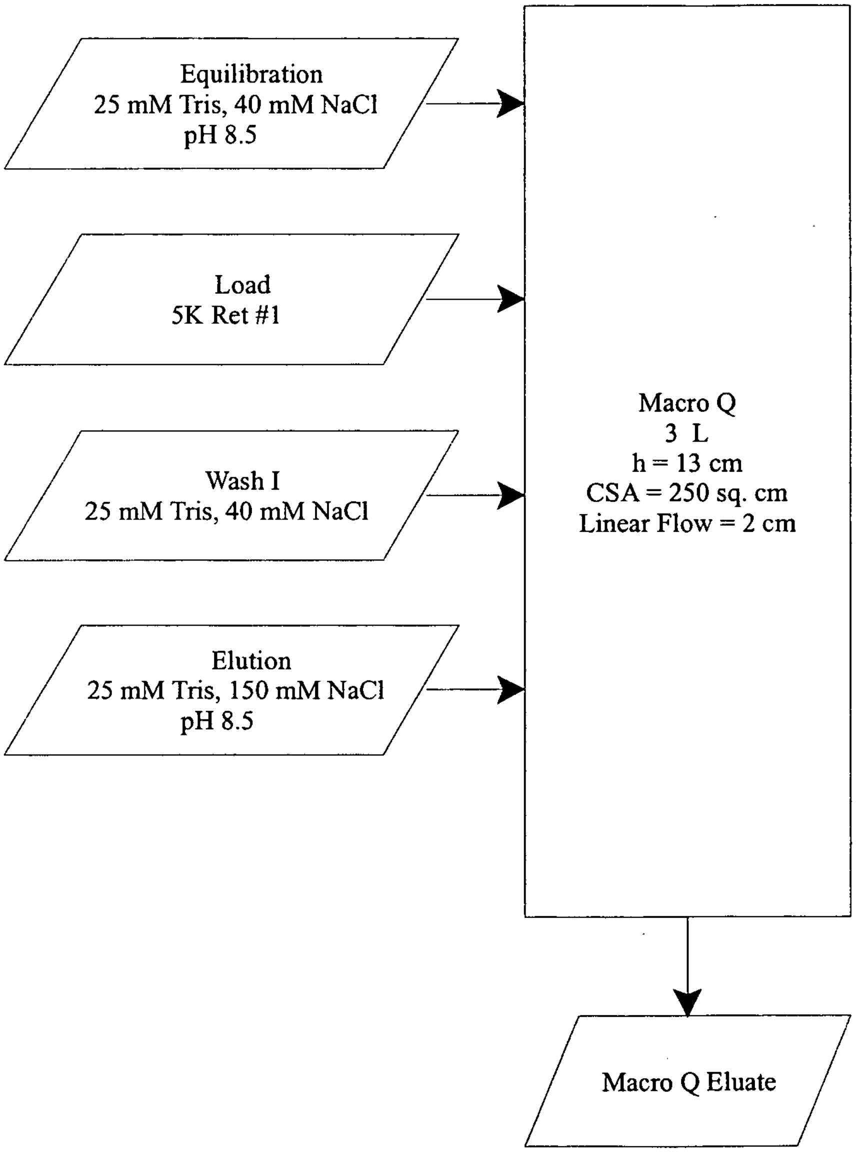
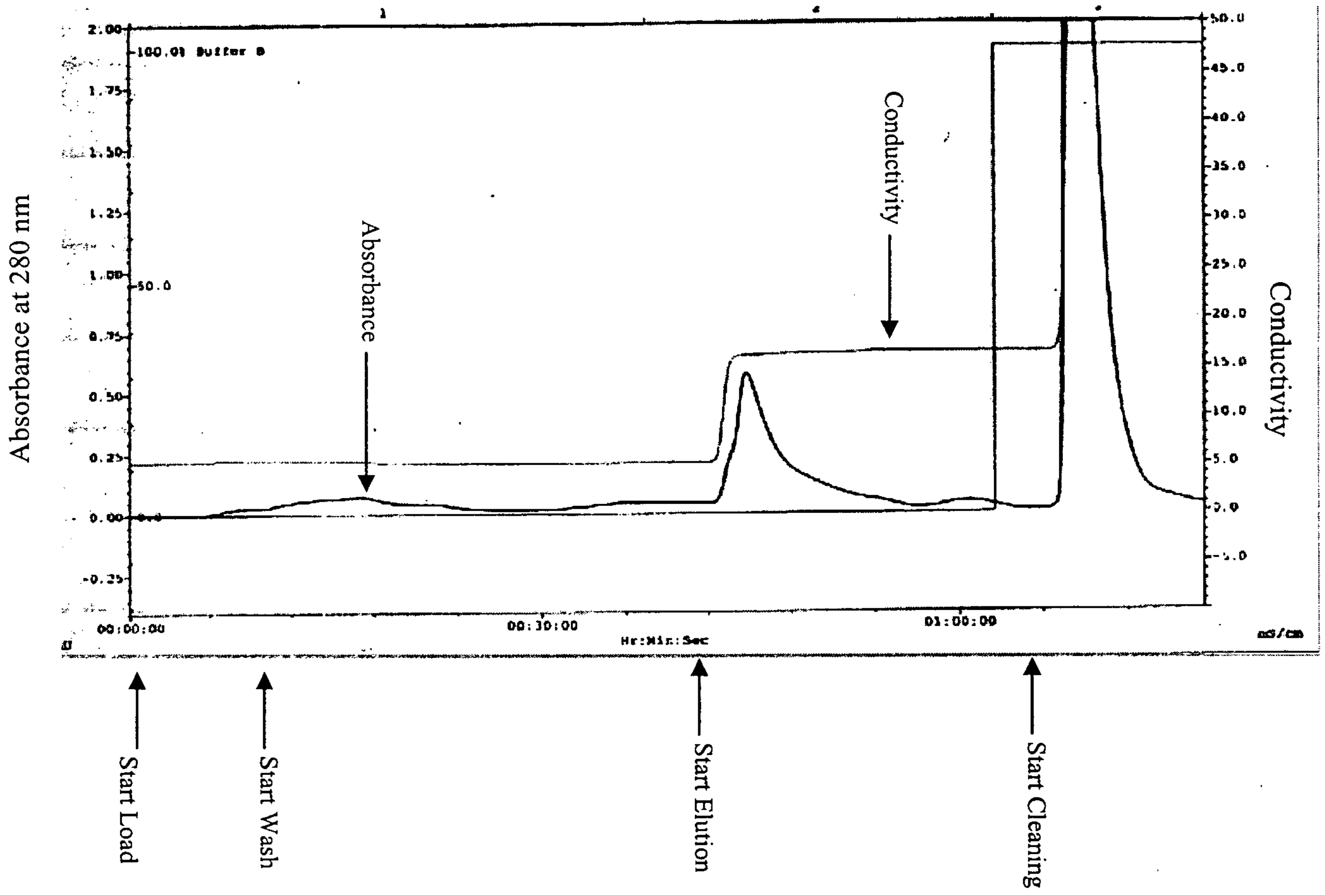

Cell Lysis,
25 mM Tris, 500 mM NaCl, pH 7.0
15000-18000 psi
Centrifugation
15000 x g, 60 min.
25 mM Tris,
40 mM NaCl
pH 7.0
Constant volume diafiltration, (10x)
100,000 NMWCO Membrane
2.5 sq. m Surface Area
Permeate, 100 K Membrane
Concentration
of 100 K Permeate,
5000 NMWCO Membrane
2.5 sq. m Surface Area
25 mM Tris,
40 mM NaCl
pH 8.5
Constant Volume
Diafiltration (5x)
5K Ret #1

Fig. 11a


Equilibration
25 mM Tris, 40 mM NaCl
pH 8.5
Load
5K Ret #1
Wash I
25 mM Tris, 40 mM NaCl
Elution
25 mM Tris, 150 mM NaCl
pH 8.5
Macro Q
3 L
h = 13 cm
CSA = 250 sq. cm
Linear Flow = 2 cm
Macro Q Eluate

09895715.070201

Fig. 11b



09985915.070204

Fig. 12

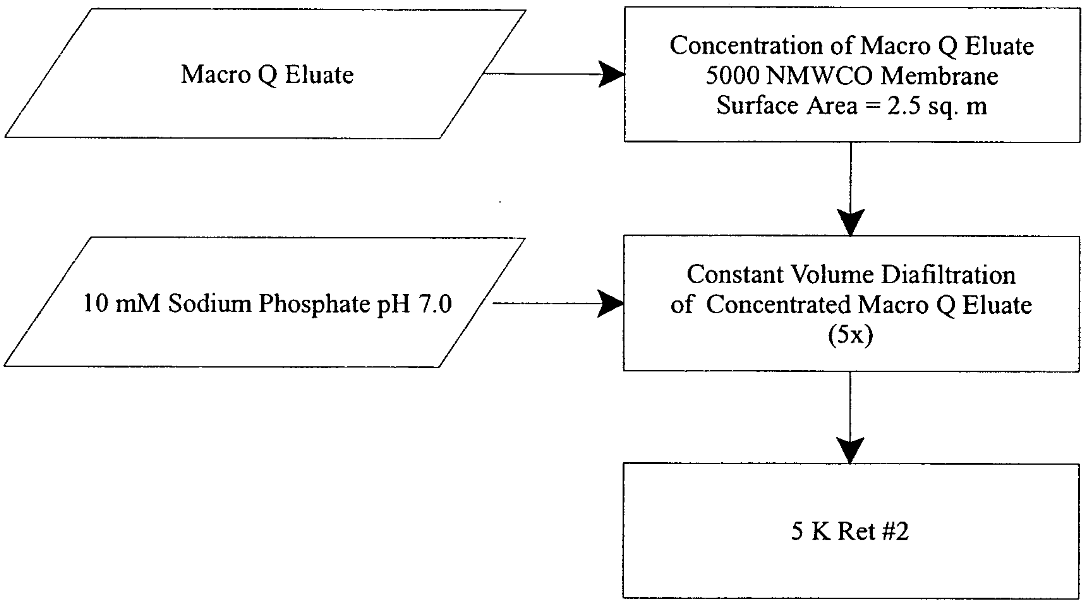

Macro Q Eluate
Concentration of Macro Q Eluate
5000 NMWCO Membrane
Surface Area = 2.5 sq. m
10 mM Sodium Phosphate pH 7.0
Constant Volume Diafiltration
of Concentrated Macro Q Eluate
(5x)
5 K Ret #2

Fig. 13a

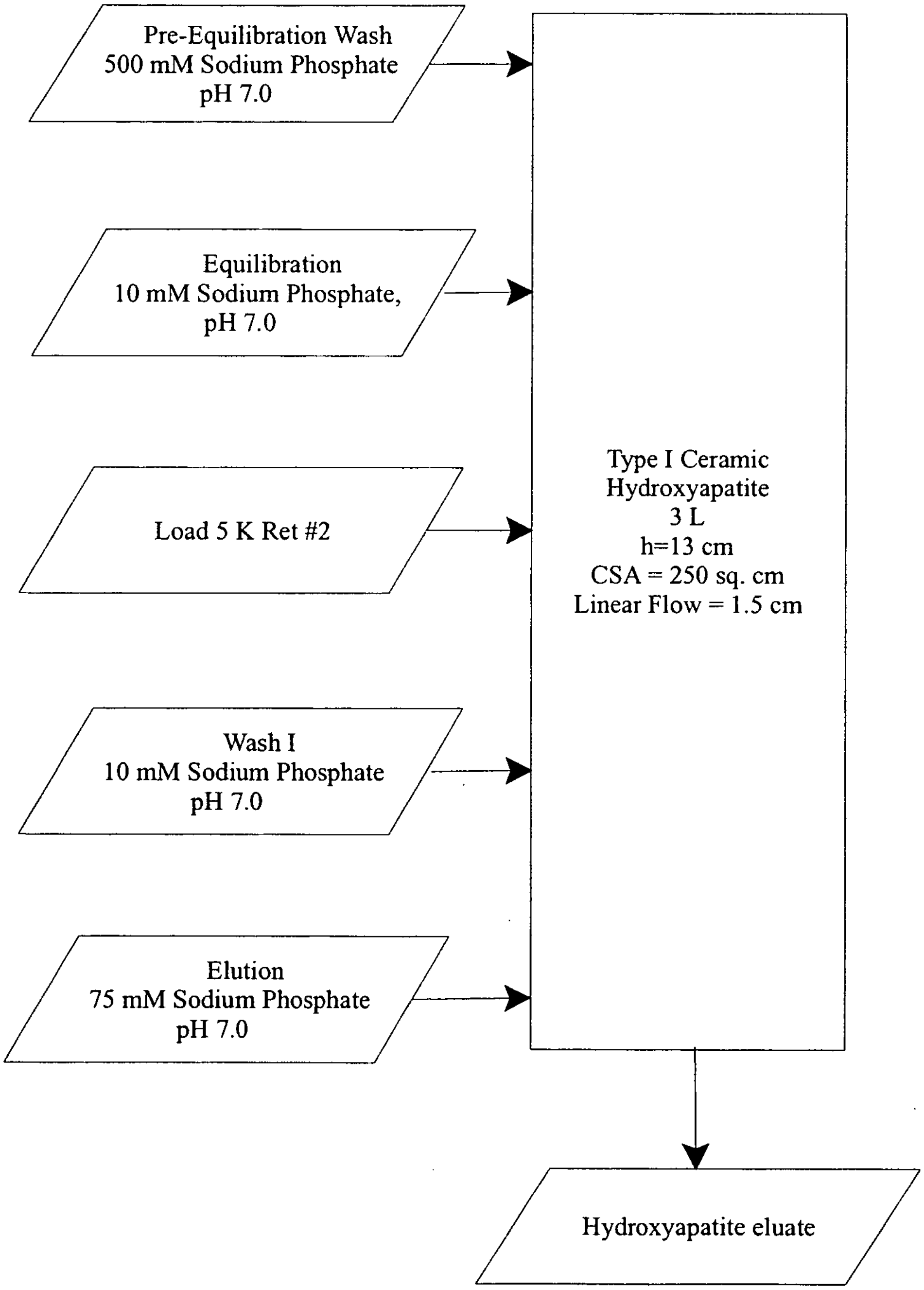
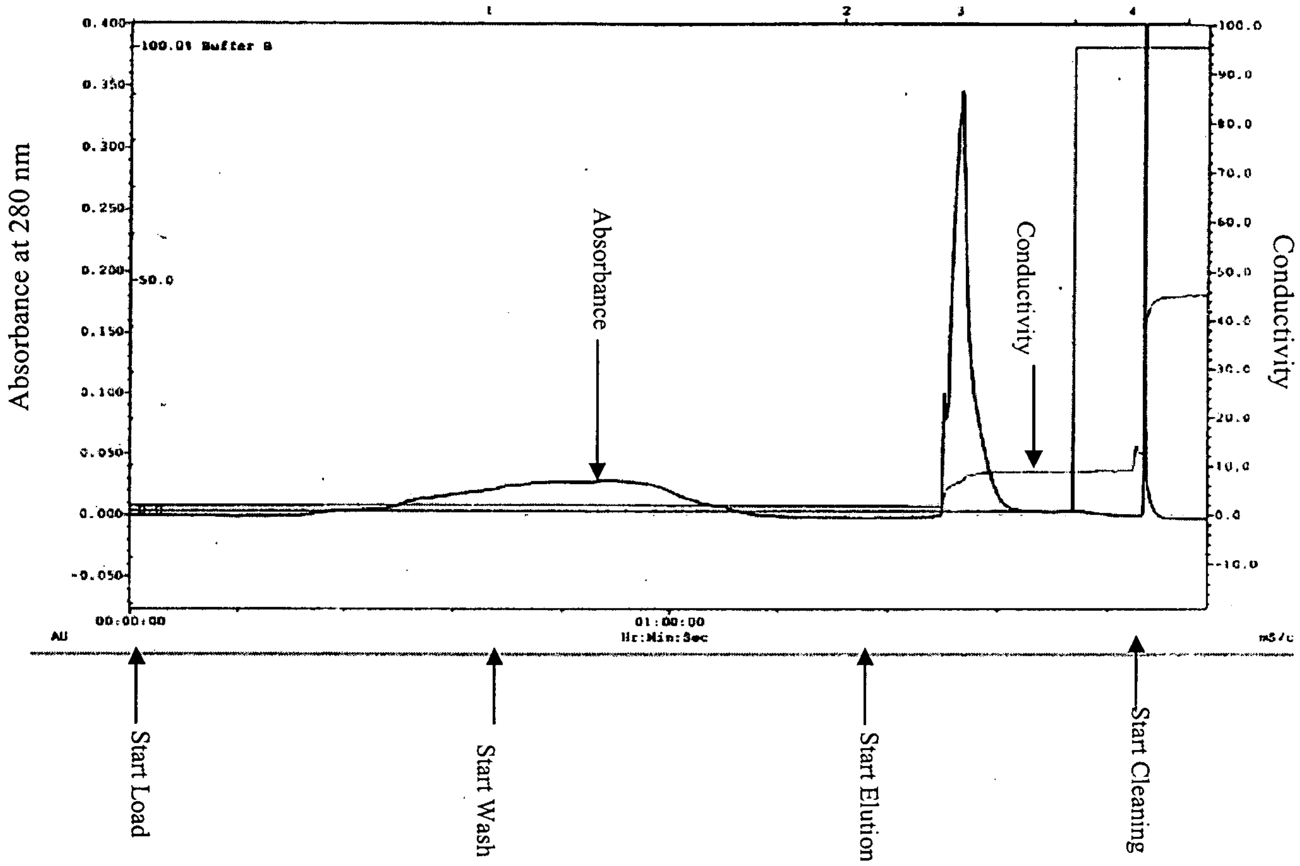

Pre-Equilibration Wash
500 mM Sodium Phosphate
pH 7.0
Equilibration
10 mM Sodium Phosphate,
pH 7.0
Load 5 K Ret #2
Wash I
10 mM Sodium Phosphate
pH 7.0
Elution
75 mM Sodium Phosphate
pH 7.0
Type I Ceramic
Hydroxyapatite
3 L
h=13 cm
CSA = 250 sq. cm
Linear Flow = 1.5 cm
Hydroxyapatite eluate

Fig. 13b



09898616.070201

Fig. 14a

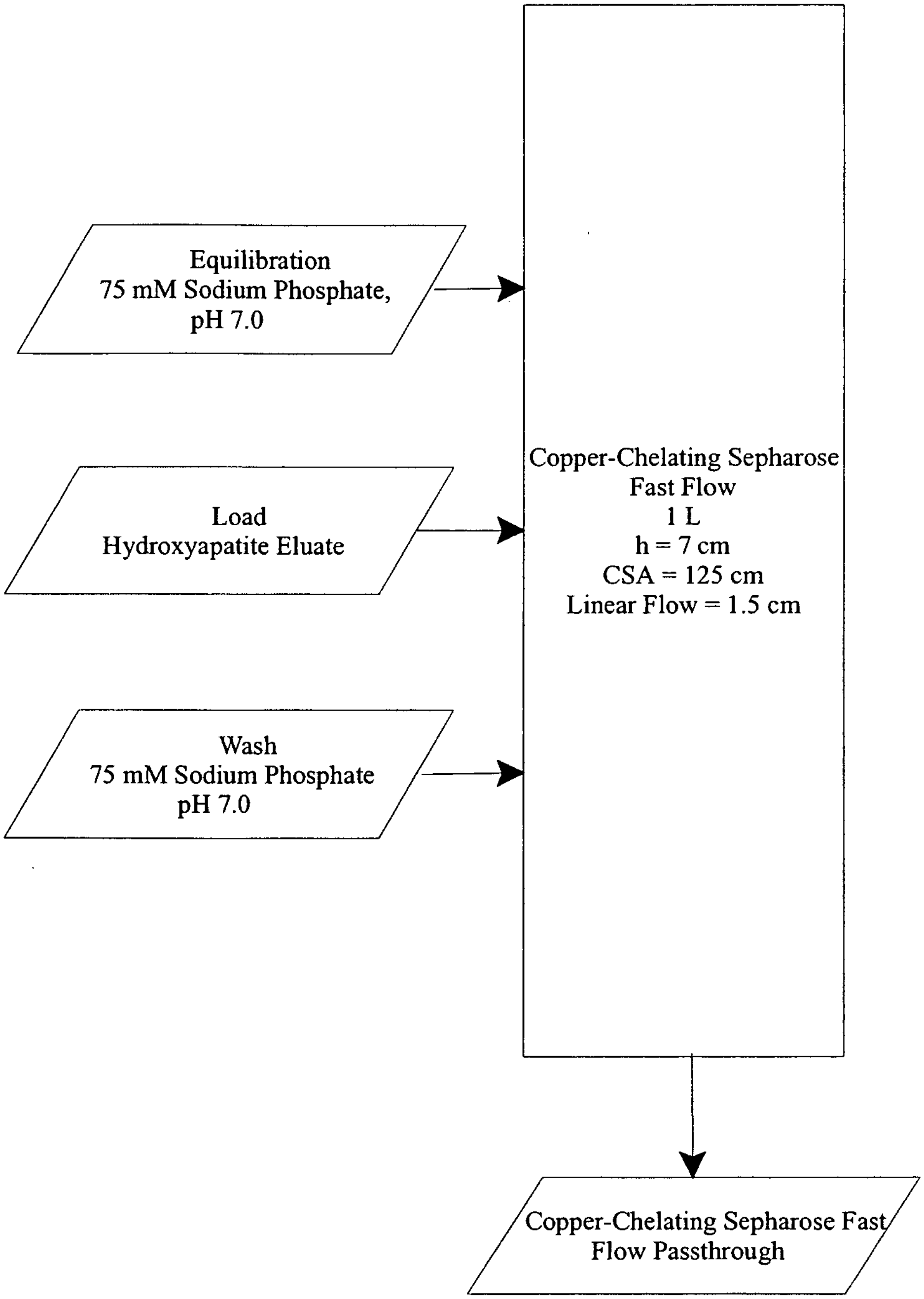

Equilibration
75 mM Sodium Phosphate,
pH 7.0
Load
Hydroxyapatite Eluate
Wash
75 mM Sodium Phosphate
pH 7.0
Copper-Chelating Sepharose
Fast Flow
1 L
h = 7 cm
CSA = 125 cm
Linear Flow = 1.5 cm
Copper-Chelating Sepharose Fast
Flow Passthrough

Fig. 14b

09596150.070201

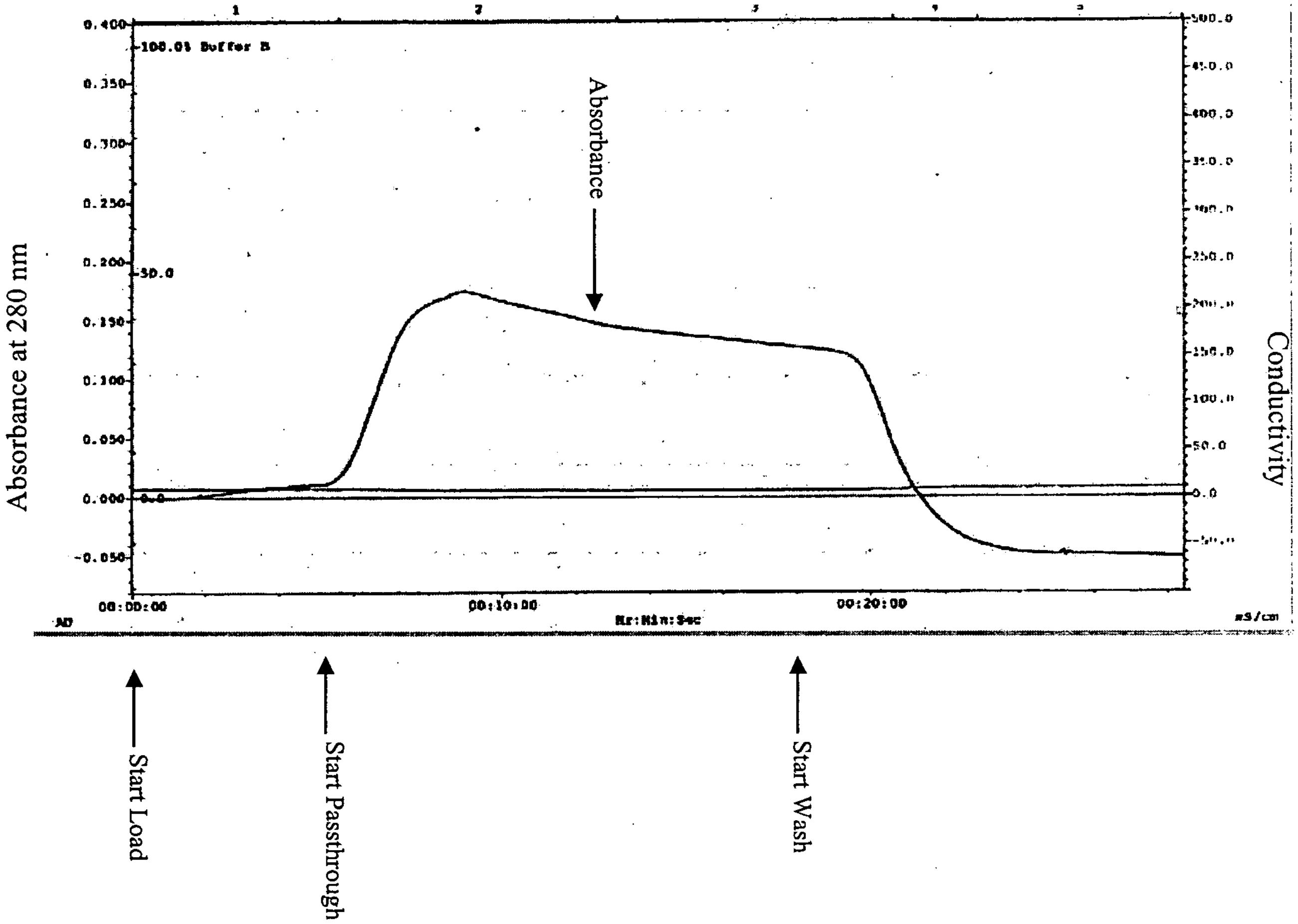


Fig. 15

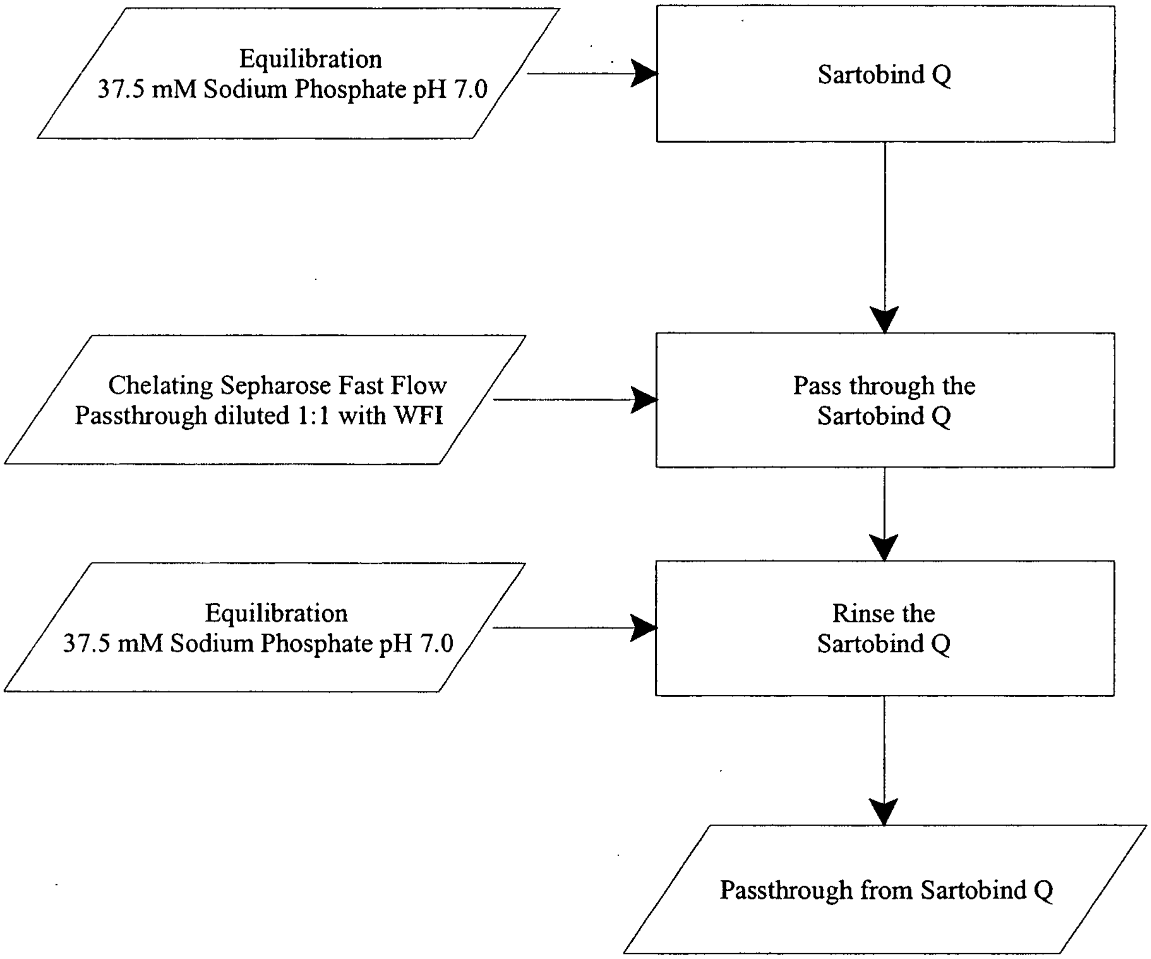
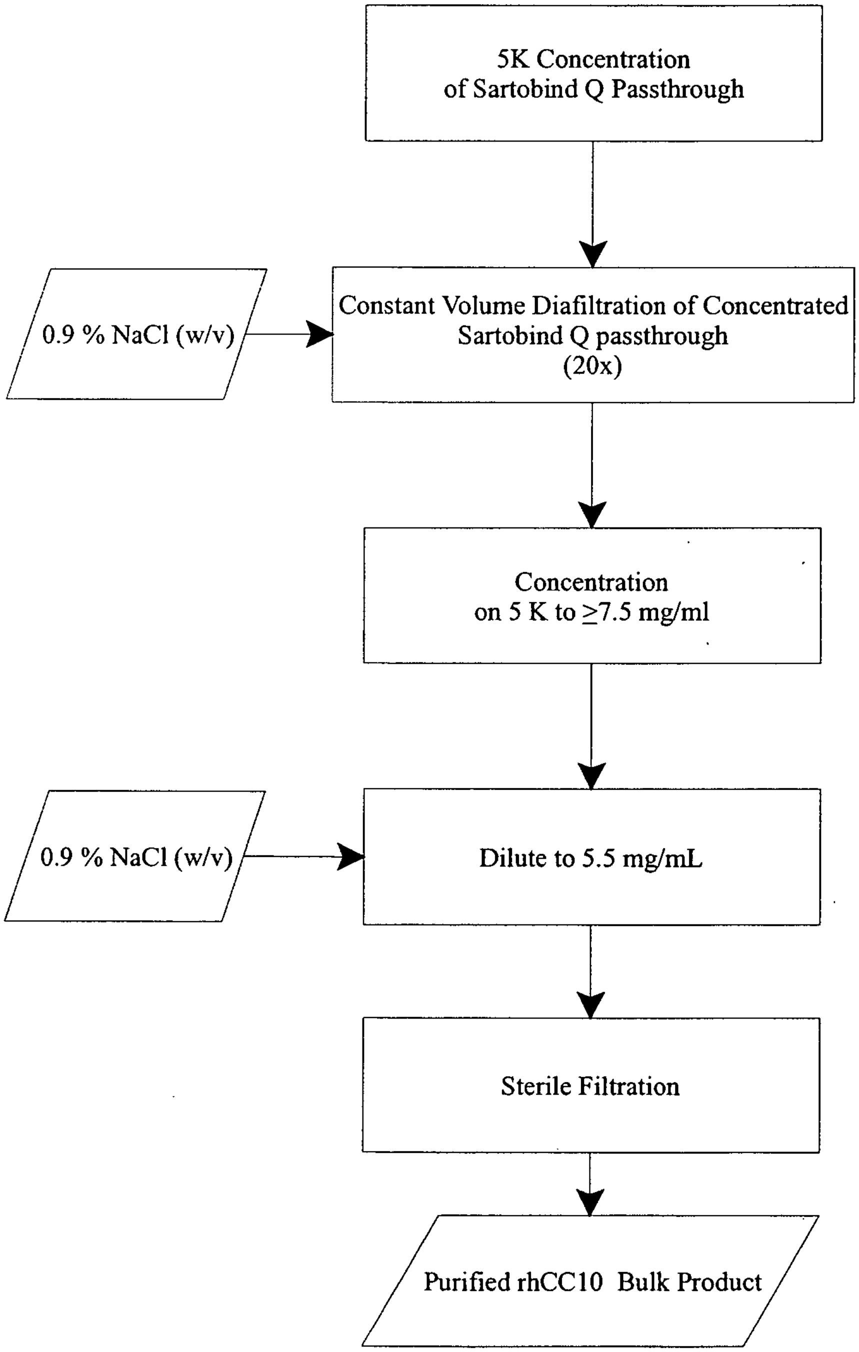
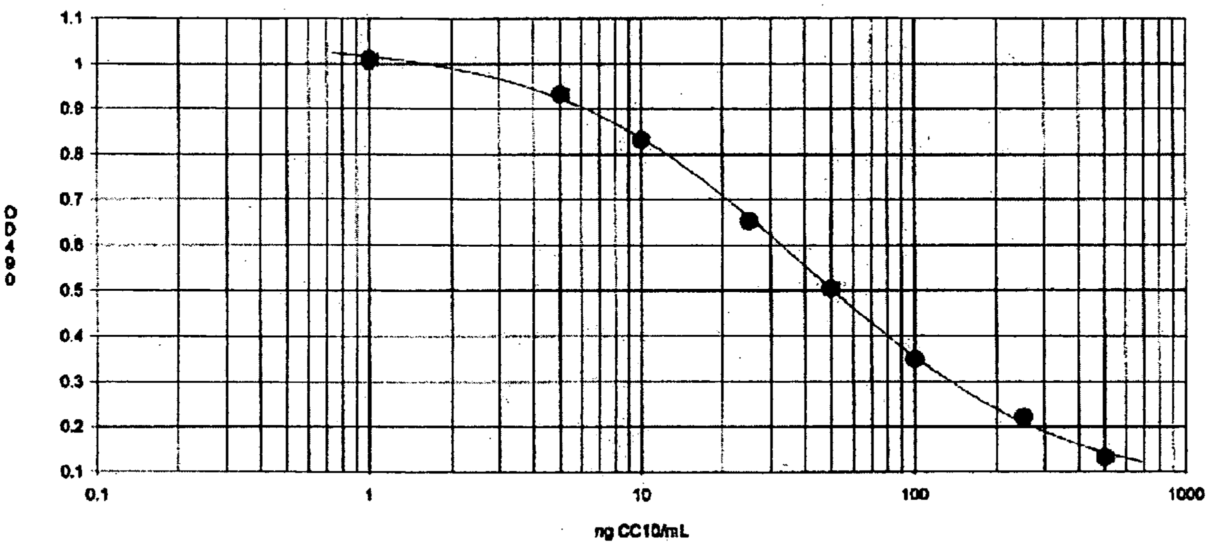

Equilibration
37.5 mM Sodium Phosphate pH 7.0
Sartobind Q
Chelating Sepharose Fast Flow
Passthrough diluted 1:1 with WFI
Pass through the
Sartobind Q
Equilibration
37.5 mM Sodium Phosphate pH 7.0
Rinse the
Sartobind Q
Passthrough from Sartobind Q

Fig. 16


5K Concentration
of Sartobind Q Passthrough
0.9 % NaCl (w/v)
Constant Volume Diafiltration of Concentrated Sartobind Q passthrough
(20x)
Concentration
on 5 K to ≥7.5 mg/ml
0.9 % NaCl (w/v)
Dilute to 5.5 mg/mL
Sterile Filtration
Purified rhCC10 Bulk Product

09898516 .070201

Fig. 17



4 Parameters y = (a-d)/(1+(x/c)^b) + d
a=1.047 b=0.9322 c=40.73 d=0.06497
R=0.9997 R^=0.9994 erri=0.007885

09898616.070201

Fig. 18

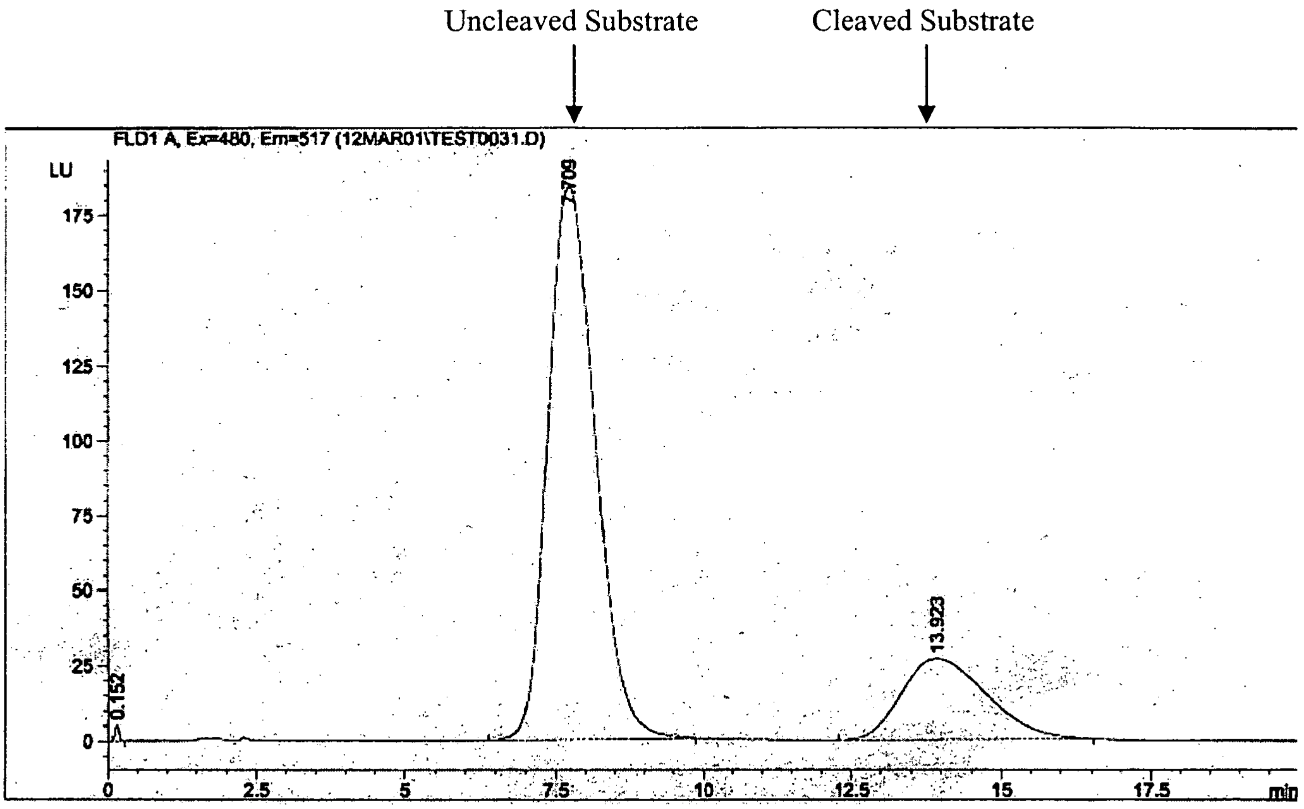
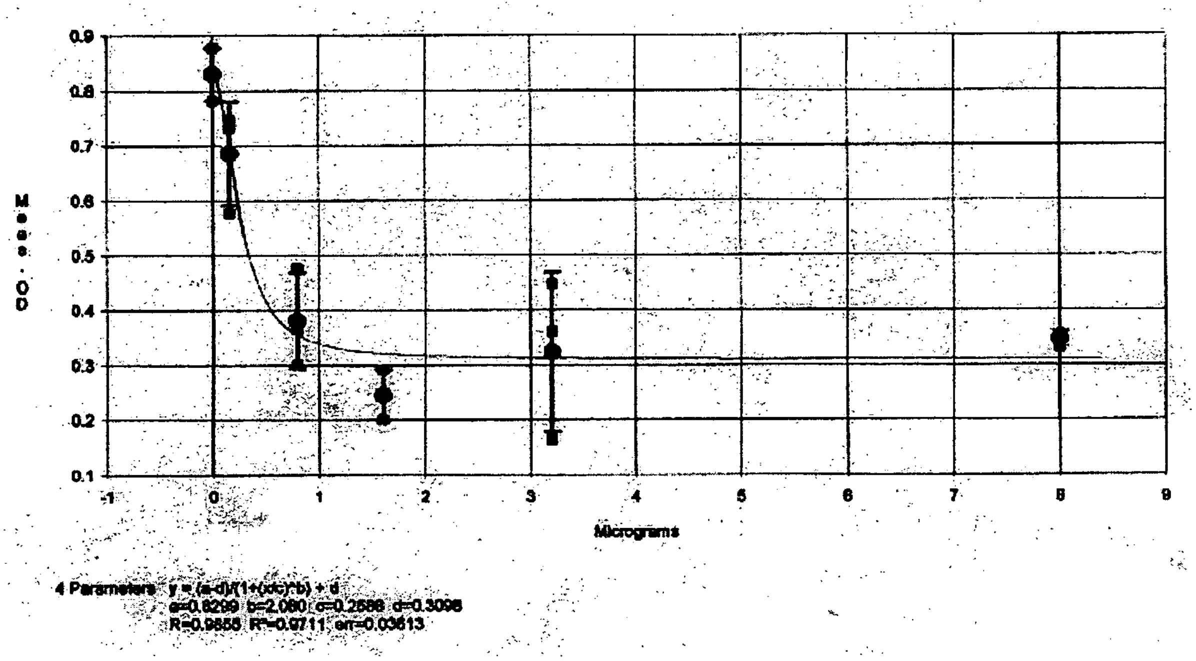
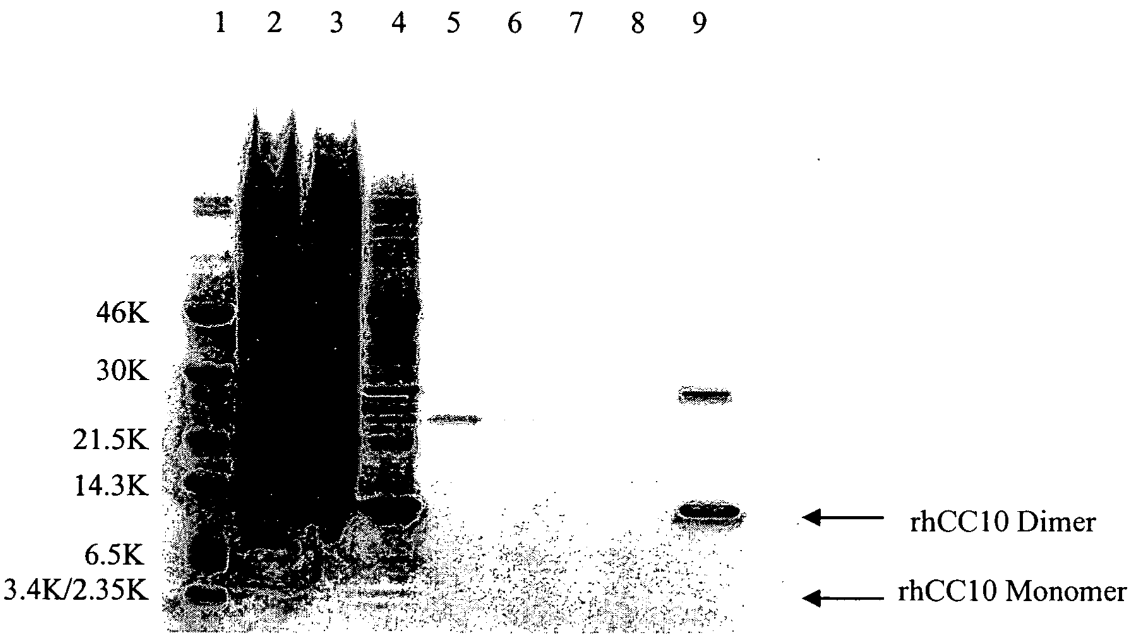

Uncleaved Substrate
Cleaved Substrate
FLD1 A, Ex=480, Em=517 (12MAR01\TEST0031.D)
LU
175
150
125
100
75
50
25
0
0.152
7.709
13.923
0
2.5
5
7.5
10
12.5
15
17.5
min

Fig. 19



09895615 .070201

Fig. 20a


1
2
3
4
5
6
7
8
9
46K
30K
21.5K
14.3K
6.5K
3.4K/2.35K
rhCC10 Dimer
rhCC10 Monomer

09868975.070201

Fig. 20b

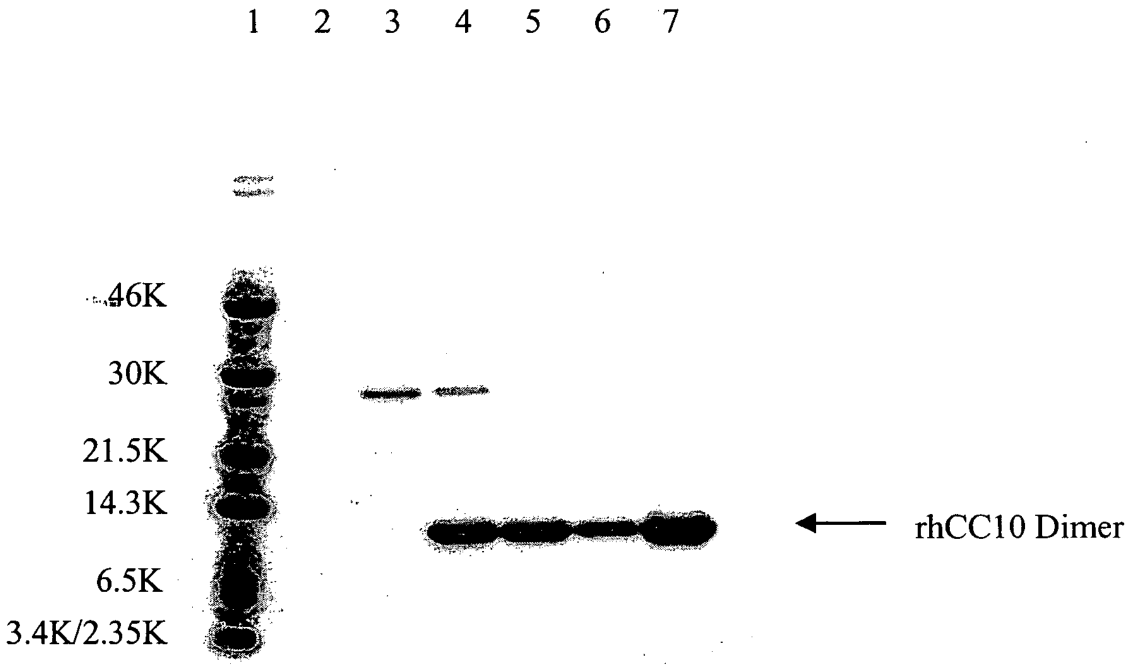

1
2
3
4
5
6
7
46K
30K
21.5K
14.3K
6.5K
3.4K/2.35K
rhCC10 Dimer

Fig. 21

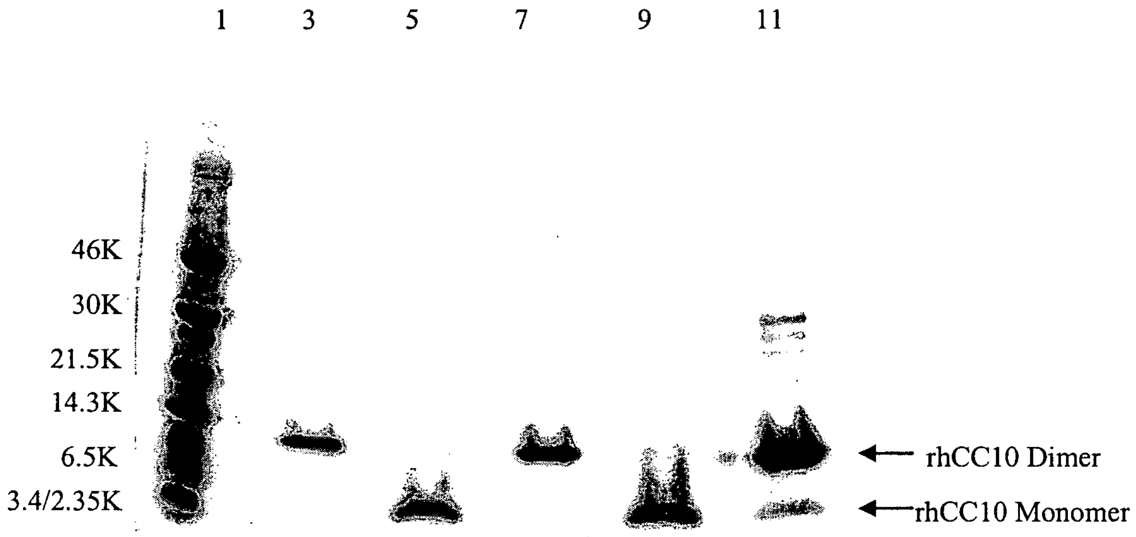
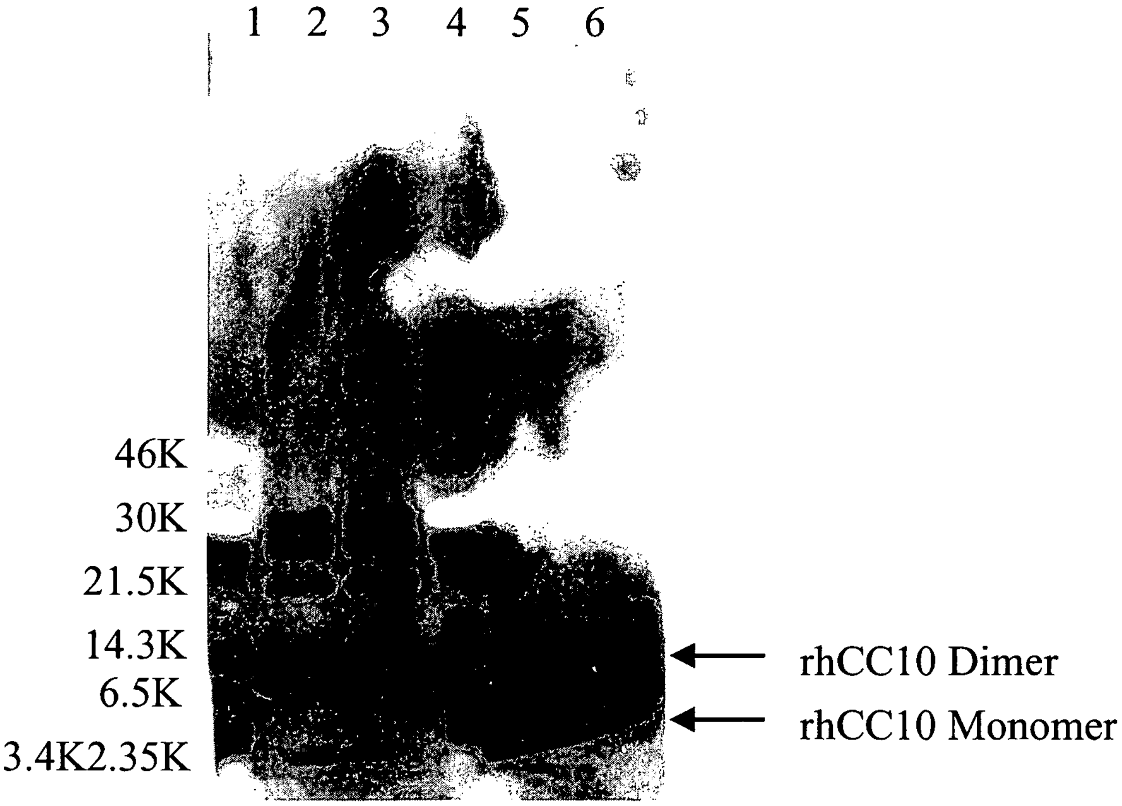
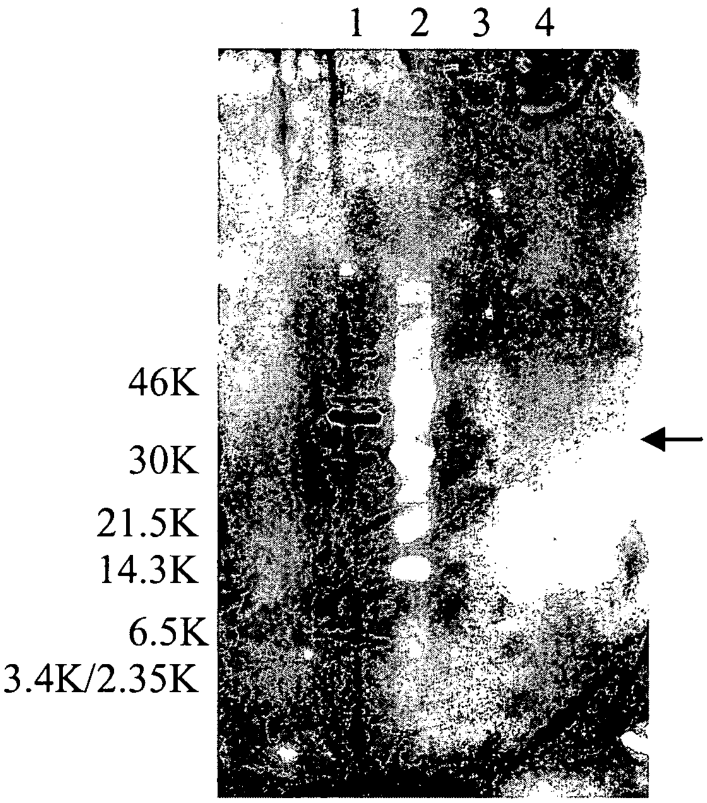

1
3
5
7
9
11
46K
30K
21.5K
14.3K
6.5K
3.4/2.35K
rhCC10 Dimer
rhCC10 Monomer

Fig. 22


1
2
3
4
5
6
46K
30K
21.5K
14.3K
6.5K
3.4K2.35K
rhCC10 Dimer
rhCC10 Monomer

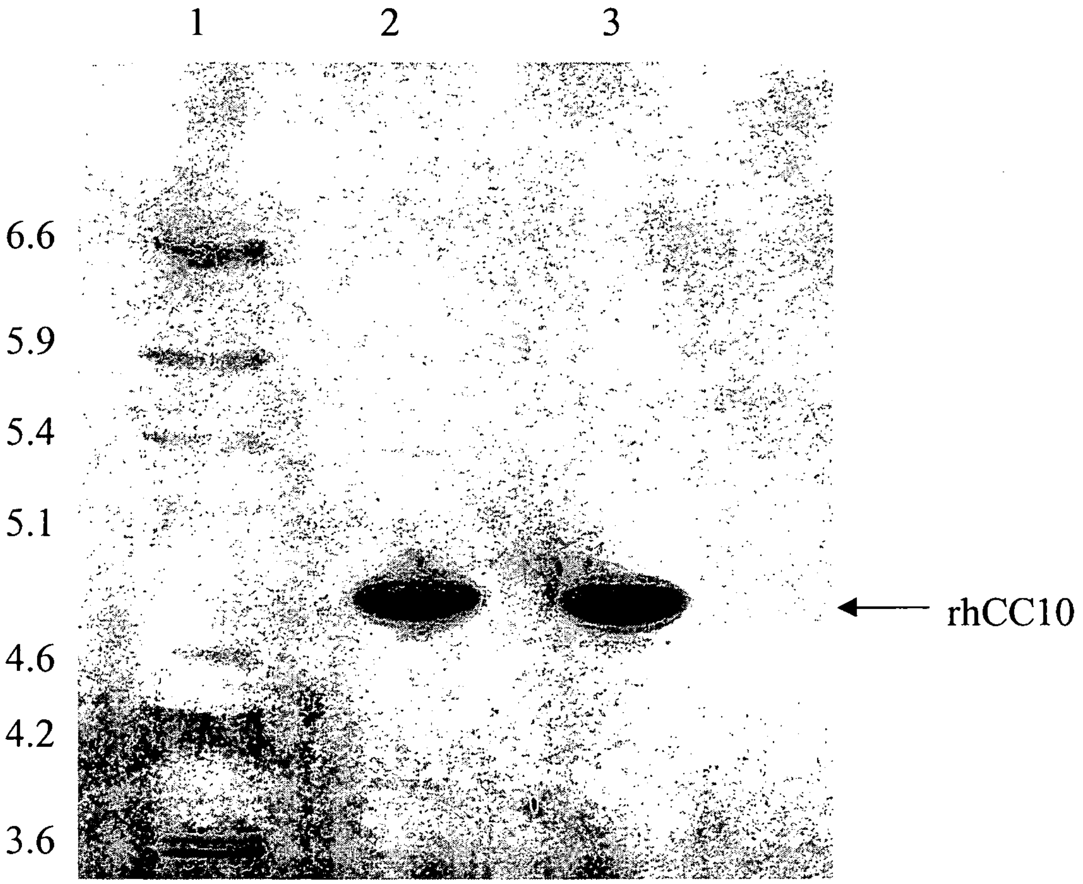
09985616.070201

Fig. 23


1
2
3
4
46K
30K
21.5K
14.3K
6.5K
3.4K/2.35K

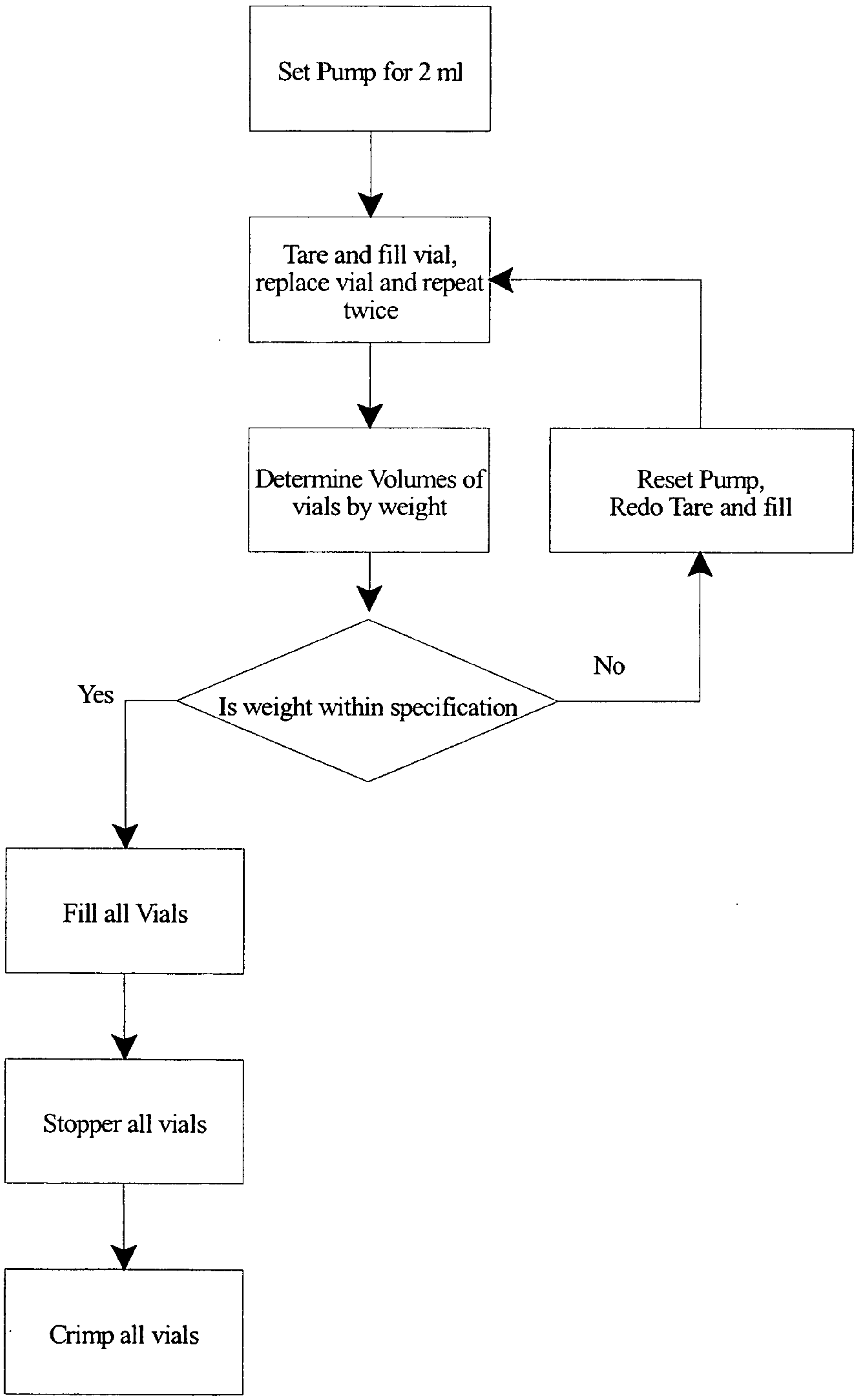
09898615.070201

Fig. 24


1
2
3
6.6
5.9
5.4
5.1
4.6
4.2
3.6
rhCC10

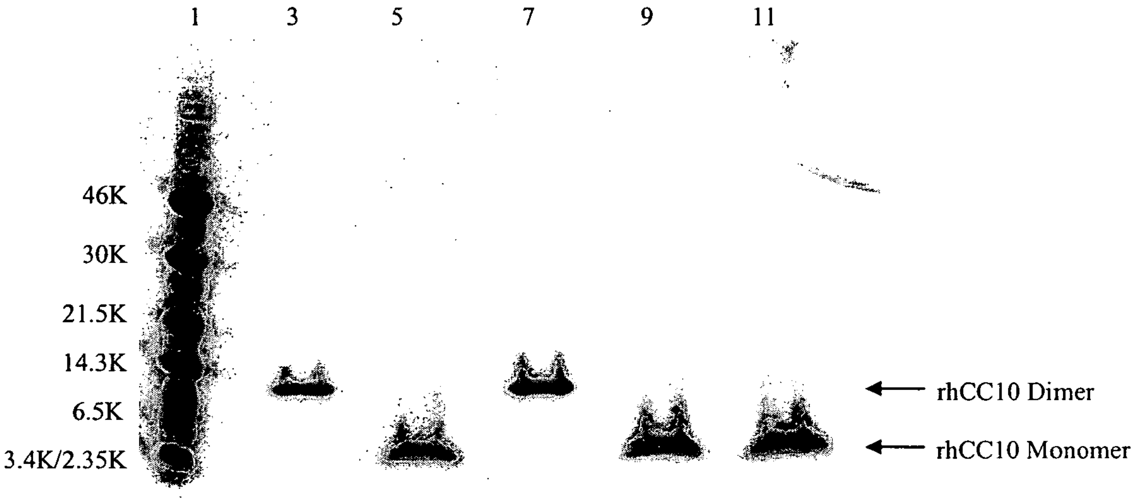
09908615.070201

Fig. 25


Set Pump for 2 ml
Tare and fill vial, replace vial and repeat twice
Determine Volumes of vials by weight
Reset Pump, Redo Tare and fill
No
Yes
Is weight within specification
Fill all Vials
Stopper all vials
Crimp all vials

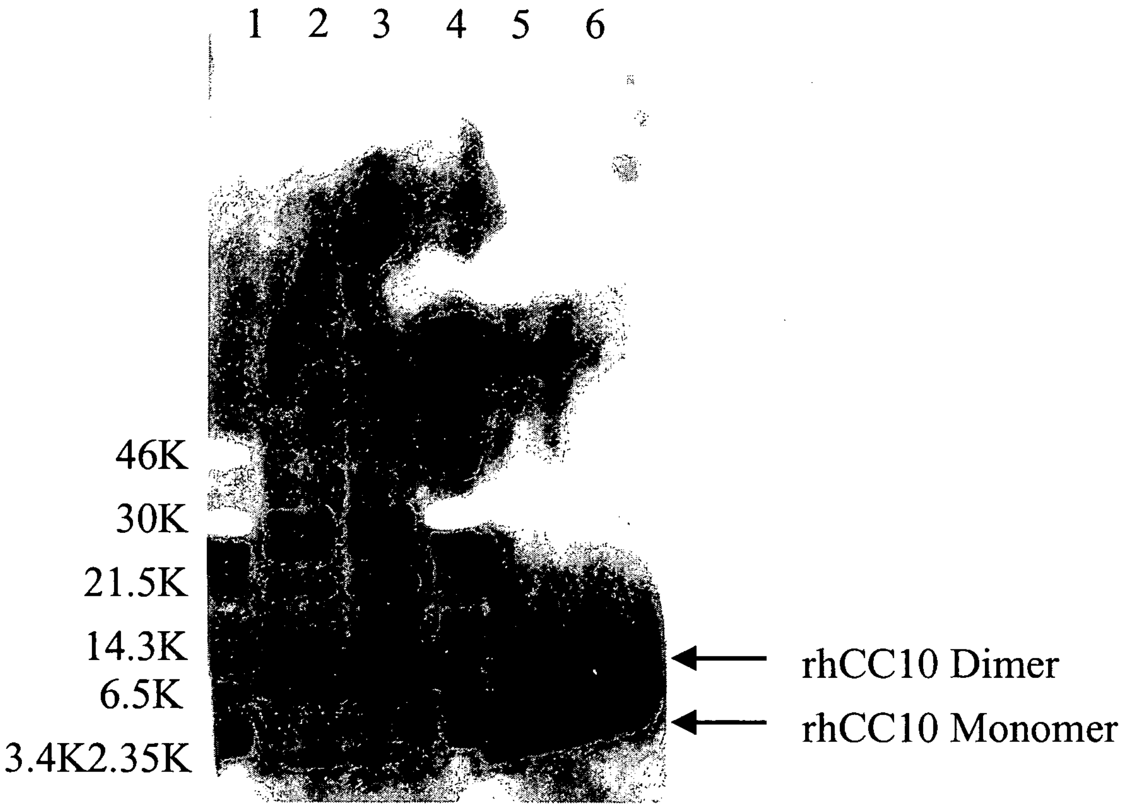
09898616 .070201

Fig. 26


1
3
5
7
9
11
46K
30K
21.5K
14.3K
6.5K
3.4K/2.35K
rhCC10 Dimer
rhCC10 Monomer

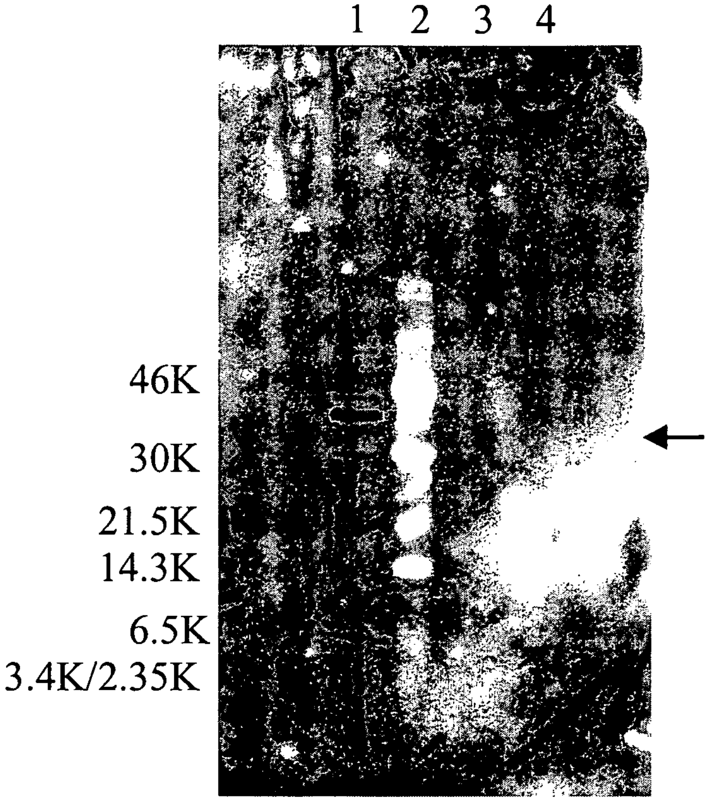
09896415.070201

Fig. 27


1
2
3
4
5
6
46K
30K
21.5K
14.3K
6.5K
3.4K2.35K
rhCC10 Dimer
rhCC10 Monomer

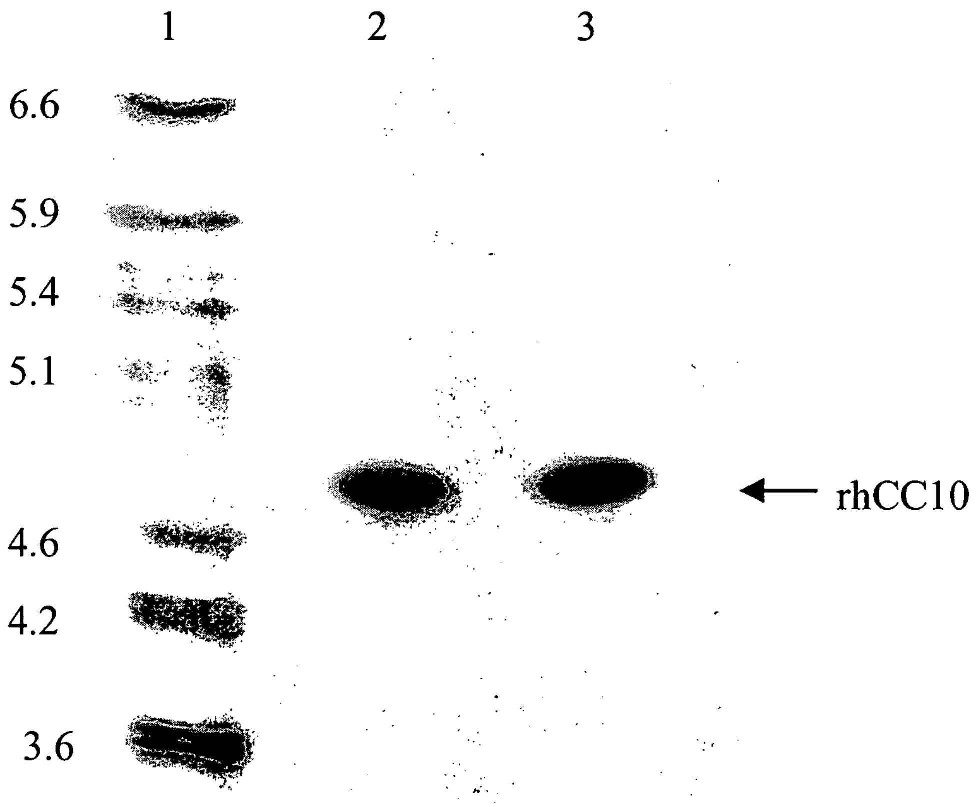
09896815 .070201

Fig. 28


1
2
3
4
46K
30K
21.5K
14.3K
6.5K
3.4K/2.35K

09956516.070201

Fig. 29


1
2
3
6.6
5.9
5.4
5.1
4.6
4.2
3.6
rhCC10

09885615 .070201

Fig. 30

```
TATGCGGTGTGAAATACCGCACAGATGCGTAAGGAGAAAATACCGCATCAGGCGCTCTTCCGCTTCCTCGCTCACTGACTCGCTGCGCTCGGTCGTTC
GGCTGCGGCGAGCGGTATCAGCTCACTCAAAGGCGGTAATACGGTTATCCACAGAATCAGGGGATAACGCAGGAAAGAACATGTGAGCAAAAGGCC
AGCAAAAGGCCAGGAACCGTAAAAAGGCCGCGTTGCTGGCGTTTTTCCATAGGCTCCGCCCCCCTGACGAGCATCACAAAAATCGACGCTCAAGTCA
GAGGTGGCGAAACCCGACAGGACTATAAAGATACCAGGCGTTTCCCCCTGGAAGCTCCCTCGTGCGCTCTCCTGTTCCGACCCTGCCGCTTACCGGAT
ACCTGTCCGCCTTTCTCCCTTCGGGAAGCGTGGCGCTTTCTCATAGCTCACGCTGTAGGTATCTCAGTTCGGTGTAGGTCGTTCGCTCCAAGCTGGGCT
GTGTGCACGAACCCCCCGTTCAGCCCGACCGCTGCGCCTTATCCGGTAACTATCGTCTTGAGTCCAACCCGGTAAGACACGACTTATCGCCACTGGCA
GCAGCCACTGGTAACAGGATTAGCAGAGCGAGGTATGTAGGCGGTGCTACAGAGTTCTTGAAGTGGTGGCCTAACTACGGCTACACTAGAAGGACA
GTATTTGGTATCTGCGCTCTGCTGAAGCCAGTTACCTTCGGAAAAAGAGTTGGTAGCTCTTGATCCGGCAAACAAACCACCGCTGGTAGCGGTGGTTT
TTTTGTTTGCAAGCAGCAGATTACGCGCAGAAAAAAAGGATCTCAAGAAGATCCTTTGATCTTTTCTACGGGGTCTGACGCTCAGTGGAACGAAAACT
CACGTTAAGGGATTTTGGTCATGAGATTATCAAAAAGGATCTTCACCTAGATCCTTTTAAATTAAAAATGAAGTTTTAAATCAATCTAAAGTATATAT
GAGTAAACTTGGTCTGACAGTTACCAATGCTTAATCAGTGAGGCACCTATCTCAGCGATCTGTCTATTTCGTTCATCCATAGTTGCCTGACTCCCCGTC
GTGTAGATAACTACGATACGGGAGGGCTTACCATCTGGCCCCAGTGCTGCAATGATACCGCGAGACCCACGCTCACCGGCTCCAGATTTATCAGCAA
TAAACCAGCCAGCCGGAAGGGCCGAGCGCAGAAGTGGTCCTGCAACTTTATCCGCCTCCATCCAGTCTATTAATTGTTGCCGGGAAGCTAGAGTAAG
TAGTTCGCCAGTTAATAGTTTGCGCAACGTTGTTGCCATTGCTACAGGCATCGTGGTGTCACGCTCGTCGTTTGGTATGGCTTCATTCAGCTCCGGTTC
CCAACGATCAAGGCGAGTTACATGATCCCCCATGTTGTGCAAAAAAGCGGTTAGCTCCTTCGGTCCTCCGATCGTTGTCAGAAGTAAGTTGGCCGCAG
TGTTATCACTCATGGTTATGGCAGCACTGCATAATTCTCTTACTGTCATGCCATCCGTAAGATGCTTTTCTGTGACTGGTGAGTACTCAACCAAGTCAT
TCTGAGAATAGTGTATGCGGCGACCGAGTTGCTCTTGCCCGGCGTCAACACGGGATAATACCGCGCCACATAGCAGAACTTTAAAAGTGCTCATCATT
GGAAAACGTTCTTCGGGGCGAAAACTCTCAAGGATCTTACCGCTGTTGAGATCCAGTTCGATGTAACCCACTCGTGCACCCAACTGATCTTCAGCATC
TTTTACTTTCACCAGCGTTTCTGGGTGAGCAAAAACAGGAAGGCAAAATGCCGCAAAAAAGGGAATAAGGGCGACACGGAAATGTTGAATACTCAT
ACTCTTCCTTTTTCAATATTATTGAAGCATTTATCAGGGTTATTGTCTCATGAGCGGATACATATTTGAATGTATTTAGAAAAATAAACAAAAGAGTTT
GTAGAAACGCAAAAAGGCCATCCGTCAGGATGGCCTTCTGCTTAATTTGATGCCTGGCAGTTTATGGCGGGCGTCCTGCCCGCCACCCTCCGGGCCGT
TGCTTCGCAACGTTCAAATCCGCTCCCGGCGGATTTGTCCTACTCAGGAGAGCGTTCACCGACAAACAACAGATAAAACGAAAGGCCCAGTCTTTCG
ACTGAGCCTTTCGTTTTATTTGATGCCTGGCAGTTCCCTACTCTCGCATGGGGAGACCCCACACTACCATCGGCGCTACGGCGTTTCACTTCTGAGTTC
GGCATGGGGTCAGGTGGGACCACCGCGCTACTGCCGCCAGGCAAATTCTGTTTTATCAGACCGCTTCTGCGTTCTGATTTAATCTGTATCAGGCTGAA
AATCTTCTCTCATCCGCCAAAACAGCCAAGCTTCACCTGCAGACAGAATTCTGTCTGCAGGTGAAGCTTCACCTGCAGACAGAATTCCGGAAGAGAG
CAAGGCTGGTGGGCGTGGACTCAAAGCATGGCAGCGGCAGAGGCTGGAGCAGTTGGGGATCTTCAGCTTCTAAATGCTAATTACACAGTGAGCTTTG
GGCTATTTTTTCCATGAGCTTAATGATGCTTTCTCTGGGCTTTTGGGGGAGGGTGTCCACCAGCTTCTTCAGCTGAGCCCCTGCCTCCCTCATGTCTTGA
TCAGGGCTGAAAAGTTCCATGGCAGCCTCATAACTGGAGGGTGTGTCCATGAGGAGGGTTTCGATGACACGCTGAAAGCTCGGGCAGATCTCTGCAG
CCATGGTGTATATCTCCTTCTTAAAGTTAACAAAATTATTTCTAGAGGGAAACCGTTGTGGTCTCCCTATAGTGAGTCGTATTAATTTGGATCCTCTAG
AGTCGACCTGCAGGCATGCCAGCTTCTGGTTCGTCGGCTGGGTGATGGCGTCGGTTTTGGCCGGCGGCGTCGGCGCGATCGCCAGCGCGAAGCAACT
GGCGTTCCTCGGCGAACATAGCGGCATGGTGGCCTTCGGCTTCTTCCGCGACCAGGTGAAGGACATGCACTGCGATGCGGACGTGATCCTGGCCCGG
TGGGATGAAAAGGCGAACTCGCCGGTGGTCTACCGCTGCCCGAAGGCGTACCTGCTCAACAGGTTCGCATCCGCGCCCTTCGTGCCCTGGCCGGACT
ACACCGAGGGGGAAAGCGAGGATCTAGGTAGGGCGCTCGCAGCGGCCCTGCGGGACGCGAAAAGGTGAGAAAAGCCGGGCACTGCCCGGCTTTATT
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CGAAGCGTGATGATGCGGTCGTGCATGCCGGCGTCACGTTTGCGGCCGGTGTAGCGGCCGGCGGCCTTCGCCAACTGGACACCCTGACGTTGACGCT
CGCGCCGATCCTCGTAGTCGTCGCGGGCCATCTGCAAGGCGAGCTTCAAAAGCATGTCCTGGACGGATTCCAGAACGATTTTCGCCACTCCGTTCGCC
TCGGCGGCCAGCTCCGACAGGTCCACCACGCCAGGCACGGCCAGCTTGGCCCCTTTGGCCCGGATCGACGCAACCAGGCGCTCGGCCTCGGCCAACG
GCAAGCGGCTGATGCGGTCGATCTTCTCCGCAACGACGACTTCACCAGGTTGCAGGTCCGCGATCATGCGCAGCAGCTCGGGCCGGTCGGCGCGTGC
GCCGGACGCCTTCTCGCGGTAGATGCCGGCGACGTAGTACCCGGCGGCCCGCGTGGCCGCTACAAGGCTCTCCTGGCGTTCAAGATTCTGCTCGTCCG
TACTGGCGCGCAGGTAGATGCGGGCGACCTTCAACCTTCGTCCCTCCGGTTGTTGCTCTCGCGTCGCCATTTCCACGGCTCGACGGCGTGCGGATCGG
ACCAGAGGCCGACGCGCTTGCCTCGCGCCTCCTGTTCGAGCCGCAGCATTTCAGGGTCGGCCGCGCGGCCGTGGAAGCGATAGGCCCACGCCATGCC
CTGGTGAACCATCGCGGCGTTGACGTTGCGCGGCTGCGGCGGCCGGCTGGCCAGCTCCATGTTGACCCACACGGTGCCCAGCGTGCGGCCGTAACGG
TCGGTGTCCTTCTCGTCGACCAGGACGTGCCGGCGGAACACCATGCCGGCCAGCGCCTGGCGCGCACGTTCGCCGAAGGCTTGCCGCTTTTCCGGCGC
GTCAATGTCCACCAGGCGCACGCGCACCGGCTGCTTGTCTACCAGCACGTCGATGGTGTCGCCGTCGATGATGCGCACGACCTCGCCGCGCAGCTCG
GCCCATGCCGGCGAGGCAACGACCAGGACGGCCAGCGCGGCAGCGGCGCGCAGCATGGCGTAGCTTCGGCGCTTCATGCGTGGCCCCATTGCTGATG
ATCGGGGTACGCCAGGTGCAGCACTGCATCGAAATTGGCCTTGCAGTAGCCGTCCAGCGCCACCCGCGAGCCGAACGCCGGCGAAAGGTACTCGACC
AGGCCGGGCCGGTCGCGGACCTCGCGCCCCAGGACGTGGATGCGCCGGCCGCGTGTGCCGTCGGGTCCAGGCACGAAGGCCAGCGCCTCGATGTTGA
AGTCGATGGATAGAAGTTGTCGGTAGTGCTTGGCCGCCCTCATCGCGTCCCCCTTGGTCAAATTGGGTATACCCATTTGGGCCTAGTCTAGCCGGCAT
GGCGCATTACAGCAATACGCAATTTAAATGCGCCTAGCGCATTTTCCCGACCTTAATGCGCCTCGCGCTGTAGCCTCACGCCCACATATGTGCTAATG
TGGTTACGTGTATTTTATGGAGGTTATCCAATGAGCCGCCTGACAATCGACATGACGGACCAGCAGCACCAGAGCCTGAAAGCCCTGGCCGCCTTGC
AGGGCAAGACCATTAAGCAATACGCCCTCGAACGTCTGTTCCCCGGTGACGCTGATGCCGATCAGGCATGGCAGGAACTGAAAACCATGCTGGGGAA
CCGCATCAACGATGGGCTTGCCGGCAAGGTGTCCACCAAGAGCGTCGGCGAAATTCTTGATGAAGAACTCAGCGGGGATCGCGCTTGACGGCCTACA
TCCTCACGGCTGAGGCCGAAGCCGATCTACGCGGCATCATCCGCTACACGCGCCGGGAGTGGGGCGCGGCGCAGGTGCGCCGCTATATCGCTAAGCT
GGAACAGGGCATAGCCAGGCTTGCCGCCGGCGAAGGCCCGTTTAAGGACATGAGCGAACTCTTTCCCGCGCTGCGGATGGCCCGCTGCGAACACCAC
TACGTTTTTTGCCTGCCGCGTGCGGGCGAACCCGCGTTGGTCGTGGCGATCCTGCATGAGCGCATGGACCTCATGACGCGACTTGCCGACAGGCTCAA
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GGGACTGTTGGGCGCCATCTCCTTGCATGCACCATTCCTTGCGGCGGCGGTGCTCAACGGCCTCAACCTACTACTGGGCTGCTTCCTAATGCAGGAGT
CGCATAAGGGAGAGCGTCGACCGATGCCCTTGAGAGCCTTCAACCCAGTCAGCTCCTTCCGGTGGGCGCGGGGCATGACTATCGTCGCCGCACTTAT
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GCCGGCATGGCGGCCGACGCGCTGGGCTACGTCTTGCTGGCGTTCGCGACGCGAGGCTGGATGGCCTTCCCCATTATGATTCTTCTCGCTTCCGGCGG
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ACTTCGATCATTGGACCGCTGATCGTCACGGCGATTTATGCCGCCTCGGCGAGCACATGGAACGGGTTGGCATGGATTGTAGGCGCCGCCCTATACCT
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GCGGCGCATCTCGGGCAGCGTTGGGTCCTGGCCACGGGTGCGCATGATCGTGCTCCTGTCGTTGAGGACCCGGCTAGGCTGGCGGGGTTGCCTTACTG
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CCGTGTTTCGTAAAGTCTGGAAACGCGGAAGTCAGCGCCCTGCACCATTATGTTCCGGATCTGCATCGCAGGATGCTGCTGGCTACCCTGTGGAACAC
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CGCGGATGAACAGGCAGACATCTGTGAATCGCTTCACGACCACGCTGATGAGCTTTACCGCAGCTGCCTCGCGCGTTTCGGTGATGACGGTGAAAAC
CTCTGACACATGCAGCTCCCGGAGACGGTCACAGCTTGTCTGTAAGCGGATGCCGGGAGCAGACAAGCCCGTCAGGGCGCGTCAGCGGGTGTTGGCG
GGTGTCGGGGCGCAGCCATGACCCAGTCACGTAGCGATAGCGGAGTGTATACTGGCTTAACTATGCGGCATCAGAGCAGATTGTACTGAGAGTGCAC
CA
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Fig. 31

Met Ala Ala Glu Ile Cys Pro Ser Phe Gln Arg Val Ile Glu Thr Leu Leu Met Asp Thr Pro Ser Ser Tyr Glu
Ala Ala Met Glu Leu Phe Ser Pro Asp Gln Asp Met Arg Glu Ala Gly Ala Gln Leu Lys Lys Leu Val Asp
Thr Leu Pro Gln Lys Pro Arg Glu Ser Ile Ile Lys Leu Met Glu Lys Ile Ala Gln Ser Ser Leu Cys Asn

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